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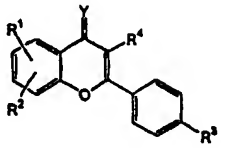
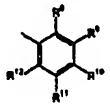


(I)



(a)

(b)

(c)

(d)

(57) Abstract

The diarylbenzopyran derivatives represented by general formula (I): wherein Y is an oxygen atom or a sulfur atom; R^1 and R^2, identical to or different from each other, are independently a hydrogen atom, a halogen atom, a C_1–C_6 lower alkyl group, a triflurometlhyl group, an alkoxy group, a hydroxy group, a nitro group, a nitrile group, or a carboxyl group; R^3 is a group of a formula: $S(O)nR^5$ wherein n is an integer of 0~2, R^5 is a hydrogen atom, a C_1–C_6 lower alkyl group, or a group of a formula: NR^6R^7 wherein R^6 and R^7, identical to or different from each other, are independently a hydrogen atom, or a C_1–C_6 lower alkyl group; R^4 is oxazolyl, benzo[b]thienyl, furanyl, thienyl, naphthyl, thiazolyl, indolyl, pyrolyl, benzofuranyl, benzodioxoyl, or a substituted group presented by structures (a), (b), (c) or (d) wherein R^8 through R^{12} identical to or different from one another, are independently a hydrogen atom, a halogen atom, a C_1–C_6 lower alkyl group, a triflurometlhyl group, an alkoxy group, a hydroxy group, a hydroxyalkyl group, a nitro group, a group of a formula: $S(O)nR^5$, a group of a formula NR^6R^7, a triflurometlhoxy group, a nitrile group, a carboxyl group, an acetyl group, or a formyl group wherein n, R^5, R^6 and R^7 have the same meaning as defined X and R^3 above; and R^{13} is a hydrogen atom, a halogen atom, a C_1–C_6 lower alkyl group, a triflurometlhyl group, an alkoxy group, a hydroxy group, a triflurometlhoxy group, a carboxyl group, or an acetyl group; or their pharmaceutically acceptable salts are disclosed. And also cyclooxygenase-2 inhibitor composition, which consists of an effective amount of a diarylbenzopyran derivative and pharmaceutically acceptable salts of diarylbenzopyran derivative and shows an excellent selective inhibition, is disclosed.

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DIARYLBENZOPYRAN DERIVATIVES AS CYCLOOXYGENASE-2 INHIBITORS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to diarylbenzopyran derivatives or their pharmaceutically acceptable salts and cyclooxygenase-2 inhibitor composition containing same.

2. Description of the Related Arts

Non-steroidal, antiinflammatory drugs(NSAIDs), which have been most prevalently used all over the world, have a problem of causing serious side-effects such as gastrointestinal tract or nephro-toxicity. NSAIDs inhibit the activity of cyclooxygenase(hereinafter "COX"), which is an enzyme involved in prostagladin synthesis, resulting in the inhibition of the biosynthesis of prostaglandin not only in inflammatory loci but also in stomach and kidney. It has been found that COX exists in the form of isoenzymes: COX-1 and COX-2[Cell, 83,345, (1995)]. COX-1 exists in normal cells and keeps cell homeostasis and controlls the function of stomach and kidney, while COX-2 is expressed by mitogens or cytokines in pain sites where inflammation and other immunoreactions occur[J. Biol. Chem., 271,33157(1996)] and is involved in pathologic phenomenon. Therefore the toxicity of NSAIDs is due to its inhibition of the coexisting COX-1's.

To avoid this problem, selective inhibitors of COX-2 has been investigated[Nature, 367, 215(1995)]. The selective inhibitors (i) have suitable antiinflammation, pain-relieving action, antipyretic action; (ii) remove toxicity from and reduce bleeding time in gastrointestinal tract and kidney; (iii) show potential anticancer activity and reduce the induction of mechanism-related side-effect; and also (iv) lower the induction of asthma in asthmatic patients who are sensitive to conventional NSAIDs. These selective inhibitors of COX-2 also show

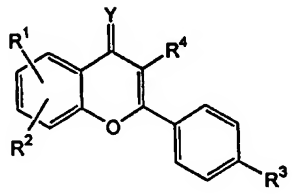
inhibition effect on smooth muscle constriction and could be used in treating Alzheimer's disease and osteoporosis of women after menopausa.

Active researches have been made on the selective inhibitors of COX-2. For example, WO 9606840, Bioorg, Med. Chem. Lett. 5, 2377(1995), Ann. Report. Med. Chem., 211(1997) and many other publications report COX-2 inhibitors having heterocyclic moiety as a base structure.

The present inventors made extensive researches to provide a new compound capable of inhibiting the COX-2's action selectively and strongly, and as a result found out that the diarylbenzopyran derivatives fulfill the requirements.

SUMMARY OF THE INVENTION

Therefore, an object of the present invention is to provide diarylbenzopyran derivatives represented by the following general formula (I) :



(I)

wherein

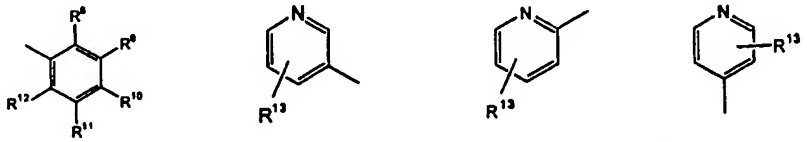
Y is an oxygen atom or a sulfur atom;

R^1 and R^2, identical to or different from each other, are independently a hydrogen atom, a halogen atom, a C_1 - C_6 lower alkyl group, a trifluromethyl group, an alkoxy group, a hydroxy group, a nitro group, a nitrile group, or a carboxyl group;

R^3 is a group of a formula : S(O)nR^5 wherein n is an integer of 0 ~ 2, R^5 is a hydrogen atom, a C_1 -C_6 lower alkyl group, or a group of a formula : NR^6R^7 wherein R^6 and R^7, identical to or different from each other, are independently a

hydrogen atom, or a C_1 -C_6 lower alkyl group; and

R_4 is oxazolyl, benzo[b]thienyl, furanyl, thienyl, naphthyl, thiazolyl, indolyl, pyrolyl, benzofuranyl, benzodioxolyl, or a substituted group presented by the following structures :



, , or

wherein

R^8 through R^{12} , identical to or different from one another, are independently a hydrogen atom, a halogen atom, a C_1 - C_6 lower alkyl group, a triflurometh yl group, an alkoxy group, a hydroxy group, a hydroxyalkyl group, a nitro group, a group of a formula : S(O)nR^5, a group of a formula : NR^6 R^7 , a triflurometh oxy group, a nitrile group, a carboxyl group, an acetyl group, or a formyl group, wherein n, R^5, R^6 and R^7 have the same meaning as defined X and R^3 above; and

R^{13} is a hydrogen atom, a halogen atom, a C_1 - C_6 lower alkyl group, a triflurometh yl group, a alkoxy group, a hydroxy group, a triflurometh oxy group, a carboxyl group, or an acetyl group;

or their pharmaceutically acceptable salts.

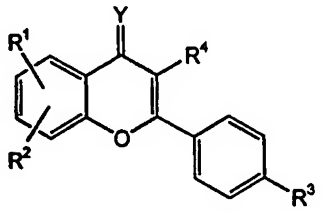
Another object of the present invention is to provide a cyclooxygenase-2 inhibitor composition comprising an effective amount of a compound represented by the above general formula(I) or pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

The diarylbenzopyran derivatives or their pharmaceutically acceptable salts of the present invention effectively and selectively inhibit COX-2's action of

biosynthesizing the prostagladin, which plays a more important role in progress of inflammation than COX-1.

The diarylbenzopyran derivatives of the present invention, which are useful as selective COX-2's inhibitor drugs, are represented by the following general formula(I) :



(I)

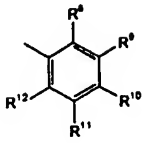
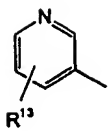
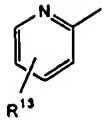
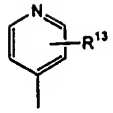
wherein

Y is an oxygen atom or a sulfur atom;

R^1 and R^2, identical to or different from each other, are independently a hydrogen atom, a halogen atom, a C_1 -C_6 lower alkyl group, a triflurometh group, an alkoxy group, a hydroxy group, a nitro group, a nitrile group, or a carboxyl group;

R^3 is a group of a formula : $S(O)nR^5$ wherein n is an integer of $0 \sim 2$, R^5 is a hydrogen atom, a C_1 -C_6 lower alkyl group, or a group of a formula : NR^6R^7 wherein R^6 and R^7, identical to or different from each other, are independently a hydrogen atom, or a C_1 -C_6 lower alkyl group;

R^4 is oxazolyl, benzo[b]thienyl, puranyl, thienyl, naphthyl, thiazolyl, indolyl, pyrolyl, benzopuranyl, benzodioxoyl, or a substituted group presented by the following structures :

, , or

wherein

R^8 through R^{12} , identical to or different from one another, are independently a hydrogen atom, a halogen atom, a C_1 - C_6 lower alkyl group, a triflurometh yl group, an alkoxy group, a hydroxy group, a hydroxyalkyl group, a nitro group, a group of a formula : S(O)nR^5, a group of a formula : NR^6 R^7 , a triflurometh oxy group, a nitrile group, a carboxyl group, an acetyl group, or a formyl group, wherein n, R^5, R^6 and R^7 have the same meaning as defined X and R^3 above; and

R^{13} is a hydrogen atom, a halogen atom, a C_1 -C_6 lower alkyl group, a triflurometh yl group, a alkoxy group, a hydroxy group, a triflurometh oxy group, a carboxyl group, or an acetyl group.

Also, the diarylbenzopyran derivatives of the above-described general formula(I) could form pharmaceutically acceptable salts, which generally refer to the salts that could form alkaline-metal salts, acid-addition salts, or base-addition salts and are pharmaceutically acceptable because of their non-toxicity. The pharmaceutically acceptable acid-addition salts of the compound(I) are derived from the organic acid or inorganic acid. The inorganic acid used in the present invention, for example, is hydrochloric acid, bromic acid, iodic acid, nitric acid, carbonic acid, sulfuric acid or phosphoric acid. The organic acid used in the present invention, for example, is formic acid, acetic acid, propionic acid, succinic acid, aspartic acid, ascorbic acid, benzoic acid, benzenesulfonic acid, methylsulfonic acid, p-toluenesulfonic acid or salicylic acid.

The pharmaceutically acceptable base-addition salts of the compound(I) are metal salts derived from Al, Ca, Li, Mg, K, Na and Zn or organic salts derived from N, N^9-dibenzylethylenediamine, choline, chloroprocaine, diethanolamine, ethylenediamine, N-methylglucamine and procaine.

Even though the use of diarylbenzopyran derivatives(I) of the present invention is not particulary limited, it is useful for treating, for example inflammatory diseases, or as analgesia for labor pain, headache or as antifebrile. The compound(I) of the present invention, not particularly limited, is also useful for treating arthritis such as rheumatic arthritis, spondylitis ankylopoietica, gouty arthritis, osteoarthritis. And the compound(I) of the present invention is useful for treating asthma, bronchitis, dysmenorrhea, tendinitis, bursitis and also useful for treating skin-related diseases such as psoriasis, eczema, burn and dermatitis. Also, the compound(I) of the present invention is useful for treating diseases such as peptic ulcer, gastritis, topical enteritis, colic diverticulitis, gastrointestinal bleeding, and the like. Also the compound(I) of the present invention coud be used in treating cancer by inhibiting the transformation of cell and the growth of metastatic cancer. Moreover, it could be used in treating and preventing diseases, which show abnormality in cyclooxygenase-involving proliferation such as diabetic retinopathy and cancerous vascularization. And it is effective in treating Alzheimer^{9}s disease and used in preventing osteoporosis and in treating glaucoma.

Also, the compound(I) of the present invention could be used as a substitute drug for conventional non-steroidal antiinflammatory drugs because it shows high activity and specificity on COX-2. Particulary, the compound of the present invention could be used as a substitute drug in treating patients who are suffering from hypoprothrombinemia, hemophilia or kidney disease, or waiting for surgery or has recurrent gastrointestinal tract disorders such as agglutination abnormality cause by anticoagulant uptake.

In addition to that the compound of the present invention, as we described above, is useful for treating human diseases, it also could be used in treating warm-blooded animals such as mice, house mice, horses, lambs, dogs, cats and etc.

Also, the compound(I) of the present invention could be used as a whole or partial substitute for the preparations containing the existing non-steroidal inflammatory drugs. In other words, diarylbenzopyran derivatives or their pharmaceutically acceptable salts could be used alone or combined with one of or some of the following components:

(i) pain relievers containing acetoaminophen or phenacetin;

(ii) potentiators containing caffeine;

(iii) H_2-antagonists;

(iv) decongestants containing aluminum hydroxide, magnesium hydroxide, simethicone, phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, propylhexedrine or levodeoxyephedrine;

(v) antitussives containing codeine, hydrocodone, caramiphene, carbetapentane or dextramethorphan;

(vi) prostaglandins containing misoprostol, enprostil, riprostil, ornoprostol or rosaprostol;

(vii) diuretics;

(viii) antihistamines having or without having sedative action.

The preferred compound(I) of the present invention includes one of the following compounds :

2-(4-(Methylsulfonyl)phenyl)-3-phenyl-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one,

3-(2-Methoxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-(N,N-Dimethylamino)phenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-(N-Methylamino)phenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
2-(4-(Methylsulfonyl)phenyl)-3-(4-trifluoromethoxyphenyl)-4H-1-benzopyran-4-one,
3-(3-Methoxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Isopropylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Ethylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Hydroxymethylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
2-(4-(Methylsulfonyl)phenyl)-3-(4-trifluoromethylphenyl)-4H-1-benzopyran-4-one,
3-(4-Hydroxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2,3-Difluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(3,5-Difluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Hydroxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2,4-Difluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2,4-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Acetylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2,4-Dimethylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Formylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Carboxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Chloro-3-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Methoxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(3,4-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Fluorophenyl)-5-methoxy-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Fluorophenyl)-5-hydroxy-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(3,5-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(N-methyl-3-pyrazolyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
6-Chloro-3-(4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4 -one,
2-(4-(methylsulfonyl)phenyl)-3-(3-nitrophenyl)-4H-1-benzopyran-4-one,
3-(3,4-Difluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
2-(4-(methylsulfonyl)phenyl)-3-(1-naphthyl)-4H-1-benzopyran-4-one,
3-(3-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(3-Chloro-4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Bromophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2,3-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(3-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(3-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
2-(4-(Methylsulfonyl)phenyl)-3-(2-oxazolyl)-4H-1-benzopyran-4-one,
6-Fluoro-2-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Benzo[b]thienyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Chloro-5-pyridinyl)-7-fluoro-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

7-Fluoro-2-(4-(methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(2-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(4-pyridinyl)-4H-1-benzopyran-4-one,

6-Fluoro-2-(4-(methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-one,

7-Fluoro-3-(2-methoxy-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(1,3-Benzodioxol-5-yl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(2-thiazolyl)-4H-1-benzopyran-4-one,

3-(Benzofuran-2-yl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(2-thienyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(2-pyrazinyl)-4H-1-benzopyran-4-one,

3-(2-Methyl-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Methoxy-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

6-Fluoro-3-(2-methyl-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

6-Fluoro-3-(2-methoxy-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Chloro-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Chloro-5-pyridinyl)-6-fluoro-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Fluoro-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

6-fluoro-3-(2-fluoro-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

7-fluoro-3-(2-fluoro-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-

4-one,
3-(4-Chloro-3-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Fluorophenyl)-6-methoxy-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
2-(4-(Methylsulfonyl)phenyl)-3-(2-trifluoromethyl-5-pyridinyl)-4H-1-benzopyran-4-one,
3-(2-Fluoro-3-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Chloro-3-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(5-Bromo-3-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Furyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(5-Indanyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Fluorophenyl)-6-methyl-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4 -one,
3-(4-Fluorophenyl)-6-hydroxy-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-methylphenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-phenyl-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(3,4-difluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(4-chloro-3-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(3-chloro-4-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(3,4-dichlorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-chlorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(3-chlorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(4-chlorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-((4-methylthio)phenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-((3,4-methylenedioxy)phenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(2,3-difluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(3-fluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(2-fluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(2,4-difluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(3-methylphenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(2-methoxyphenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(2-fluoro-5-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(4-methylphenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(4-methoxyphenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(2-methoxy-5-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(3-methoxyphenyl)-4H-1-benzopyran-4-one,.

2-(4-(Aminosulfonyl)phenyl)-3-(4-fluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(2-chloro-5-pyridinyl)-7-fluoro-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(3,5-difluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(2-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(3-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(3-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(2-chloro-5-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(2-chloro-5-pyridinyl)-6-fluoro-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(2-fluoro-5-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(2-fluoro-5-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(2-methyl-5-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(2-methoxy-5-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(2-methoxy-5-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(4-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(2-thienyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(2-furyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(4-fluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-phenyl-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(4-methylphenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(4-chlorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(3-fluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(4-fluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(3-fluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(2-fluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(3,4-dichlorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-8-chloro-3-(4-fluorophenyl)-5-hydroxy-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-8-chloro-3-(4-fluorophenyl)-5-methoxy-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-6-methoxy-3-(4-fluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-7-methoxy-3-(4-fluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-6-hydroxy-3-(4-fluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-phenyl-4H-1-benzopyran-4-thione,

3-(4-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

6-Fluoro-3-(4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4 -thione,

3-(2-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

7-Fluoro-2-(4-(methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-thione,

3-(3-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(2-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(4-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(3-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(4-Methoxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

6-Fluoro-2-(4-(methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-thione,

3-(2-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(2,3-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(3,4-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(3-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(4-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(3-Methoxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

2-(4-(Methylsulfonyl)phenyl)-3-(4-trifluoromethylphenyl)-4H-1-benzopyran-4-thione,

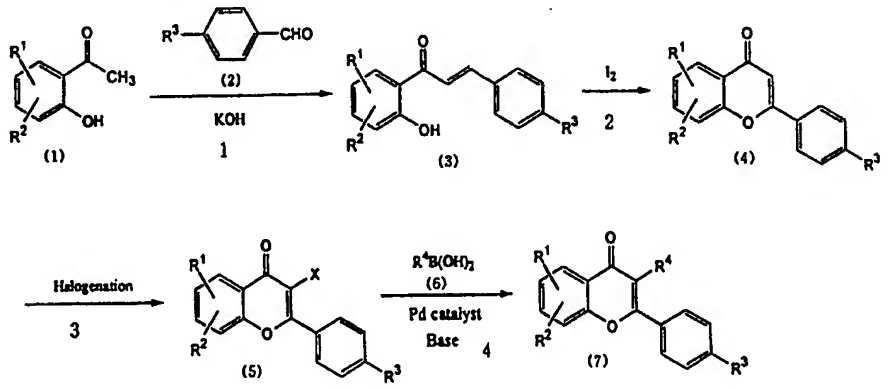
3-(3-Chloro-4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4 -thione,

2-(4-(Methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-thione,

2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(3-pyridinyl)-4H-1-benzopyran-4-thione,
2-(4-(Aminosulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-thione,
2-(4-(Aminosulfonyl)phenyl)-3-(4-fluorophenyl)-4H-1-benzopyran-4-thione,
2-(4-(Aminosulfonyl)phenyl)-3-(2-fluorophenyl)-4H-1-benzopyran-4-thione,
2-(4-(Aminosulfonyl)phenyl)-3-(4-chlorophenyl)-4H-1-benzopyran-4-thione,
2-(4-(Aminosulfonyl)phenyl)-3-phenyl-4H-1-benzopyran-4-thione,
2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(4-fluorophenyl)-4H-1-benzopyran-4-thione,
2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(3-pyridinyl)-4H-1-benzopyran-4-thione

The diarylbenzopyran derivatives of the present invention can be prepared by reaction schemes 1 through 6. Wherein R^1, R^2, R^3 and R^4 in the reaction schems have the same meanings as defined above.

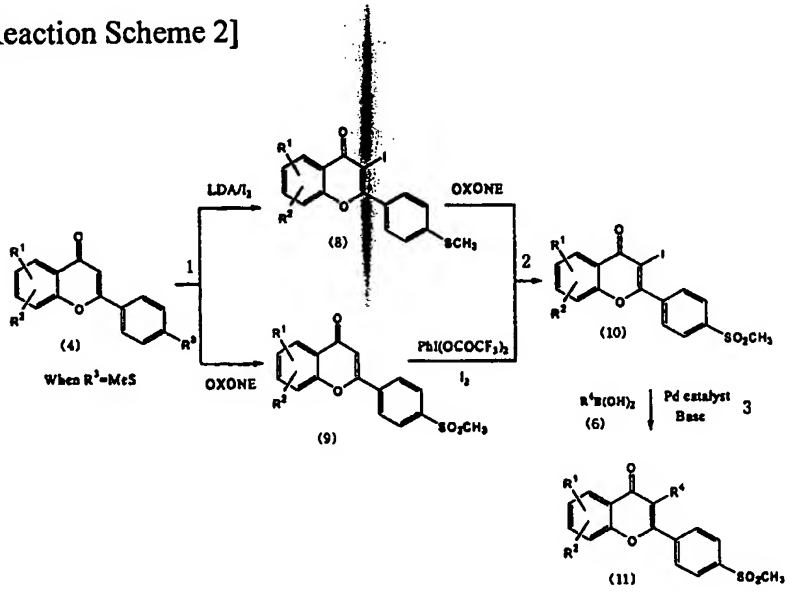
[Reaction Scheme 1]



It represents a four-step reaction of preparing diarylbenzopyran derivative. In Step 1, chalcone(3) is prepared by condensation of substituted acetophenon(1) and substituted aldehyde(2) in the presence of KOH base. In Step 2, flavone

derivative is prepared by cyclization of calcone(3) by adding I_2 as a catalyst. A suitable solvent of this step is dimethyl sulfoxide(DMSO). In Step 3, 3-halogenized flavone derivative is prepared by reaction of flavone derivative(4) either with I_2 or N-bromosuccinimide(NBS). In Step 4, benzopyran derivative(7) in which R^4 group at position 3 is substituted is prepared by cross-coupling reaction of substituted flavone derivative(5) with R^4 group substituted boronic acid using Paladium as a catalyst[(Synth. Commun., 11, 513(1981)].

[Reaction Scheme 2]

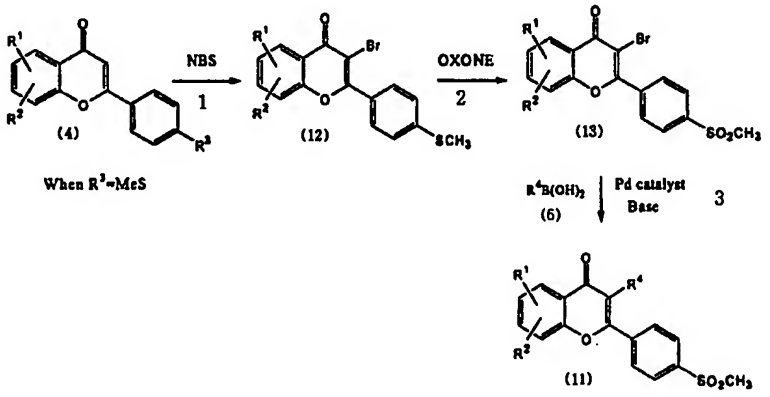


It represents a 3-step transformed reaction of preparing diarylbenzopyran derivative. In Step 1, compound(8) is prepared by the reaction of flavone derivative(4) having methylthio group as R^3 with I_2 in the presence of Lithium diisopropylamide(LDA) base, at a temperature of -78 ℃[J. Chem. Soc. Perkin Trans. I. 799(1985)]. In Step 2, methylsulfonylflavone(10) is prepared by oxidation with oxone(potassium peroxymonosulfate) or 3-chloroperoxybenzoic acid(MCPBA). In Step 3, benzopyran derivative(11) is prepared by cross-

coupling reaction of compound(10) with boronic acid(6) using paladium as catalyst.

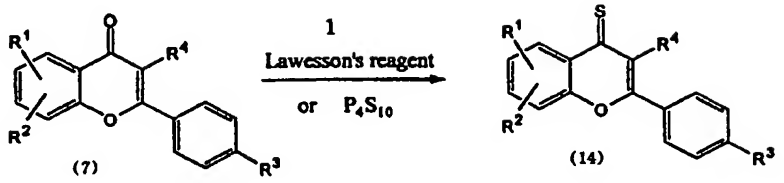
Alternatively, compound(11) could be prepared by the following method: First, methylsulfonyl group substituted flavone derivative(9) is prepared by oxidizing compound(4) having methylthio group as R^3 with oxone; and then compound(10) is prepared by reacting compound(9) with I_2 and [Bis(trifluoroacetoxy)iodo]benzene(BTI); and benzopyran derivative(11) is prepared by Step 3 of the above reaction.

[Reaction Scheme 3]



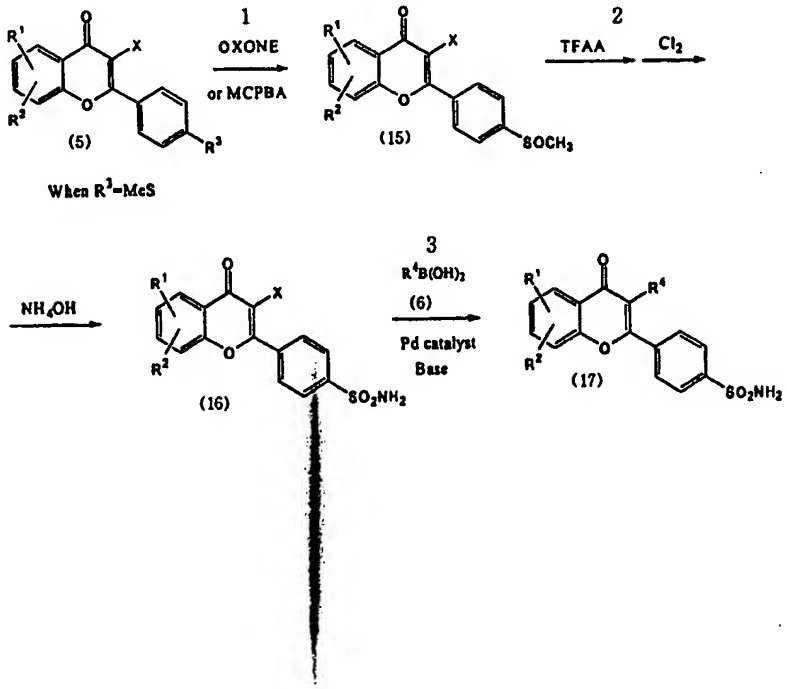
It represents the 3-step modified reaction of preparing diarylbenzopyran derivative. In Step 1, bromoflavone(12) is prepared by refluxing flavone derivative(4) having methylthio group as R^3 in chloroform in the presence of N-bromosuccinimide(NBS). In Step 2, methylsulfonylflavone(13) is prepared by oxidation with oxone or MCPBA. In Step 3, benzopyran derivative(11) is substituted is prepared by cross-coupling reaction of compound(13) with boronic acid(6) using paladium catalyst.

[Reaction Scheme 4]



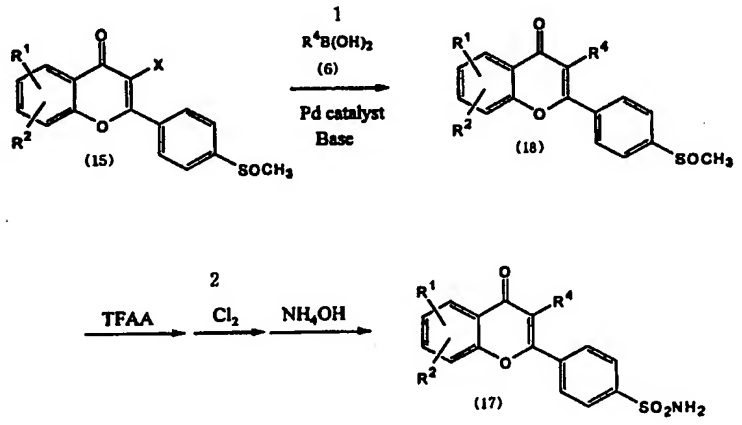
It represents the 1-step reaction of preparing diarylbenzopyranthione derivative. Benzopyranthione derivative(14) is prepared by refluxing diarylbenzopyran derivative with Lawesson reagent(2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphentan-2,4-disulfate; Org. Synth. Coll., 7, 372(1990)) or P_4S_{10} in toluenet.

[Reaction Scheme 5]



It represents the 3-step reaction of preparing diarylbenzopyran derivative. In Step 1, methylsulfinylflavone derivative(15) is prepared by oxidizing compound(5) with oxone or MCPBA. In Step 2, aminosulfonylflavone derivative is prepared by reacting flavone derivative(15) with trifluoroacetic anhydride(TFAA), chlorine gas, ammonium hydroxide. In Step 3, benzopyran derivative(17) is prepared by cross-coupling reaction of aminosulfonylflavone deriative(16) with boronic acid(6) using paladium catalyst.

[Reaction Scheme 6]



It represents the modified reaction of preparing diarylbenzopyran derivative. In Step 1, benzopyran derivative(18) is prepared by cross-coupling reaction of flavone derivative(15) prepared in reaction scheme 5, Step 1 with boronic acid(6) using paladium catalyst. In next step, benzopyran derivative(17) is prepared by having the same condition of the reaction scheme 5, Step 2.

The present invention will be described in more detail by the following examples and experimental examples, but it must not to be construed that this

invention is confined by them.

[Example 1] 3-(4-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzo-pyran-4-one

Step 1; 2'-Hydroxy-4-(methylthio)chalcone

To a solution of 2'-hydroxyacetophenone(10.88g, 80mmol) and 4-(methylthio)benzaldehyde(12.16g, 80mmol) in ethanol(120㎖) at a temperature of 0℃ was added a solution of KOH (8.96g, 2.0 equivalent) in water(40㎖) dropwise. The mixture was stirred at room temperature for 24 hours. The solution was acidified with 3N HCl(88㎖) and extracted two times with CH_2Cl_2 (100㎖ per each). The organic layer was washed with saturated NaCl and dried over anhydrous $MgSO_4$ and filtered and concentrated under reduced pressure. The recrystallization of the residue with CH_2Cl_2 and petroleum ether yielded the title compound as a yellow solid (42.01g, 65%).

mp: 98～100℃

^{1}H NMR($CDCl_3$, 300MHz): δ 7.94～7.86(2H, m), 7.65～7.47(6H, m), 7.29～7.25(2H, m), 7.05～6.92(2H, m), 2.53(3H, s)

IR(KBr): 2911, 1658, 1433, 1306, 1090, 1013㎝$^{-1}$

Step 2 : 2-(4-(Methylthio)phenyl)-4H-1-benzopyran-4-one

2'-hydroxy-4-(methylthio)chalcone(9.5g, 35.15mmol) from Step 1 and catalytic amount of I_2 was dissolved in dimethylsulfoxide(;DMSO, 100㎖) and the resulting mixture was stirred at a temperature of 180℃ for half an hour. After identifying the reaction being complete by TLC, the resulting dark solution was poured into excessive ice-water(about 300㎖) and stirred for 10 minutes. The mixture was extracted two times with CH_2Cl_2 (100㎖ per each). And the organic

layer was washed with saturated $Na_2S_2O_3$(100㎖) , brine and dried over anhydrous $MgSO_4$ and filtered and concentrated under reduced pressure. The recrystallization of the residue with CH_2Cl_2 and petroleum ether yielded the title compound as a light yellow solid(7.54g, 80%).

mp : 110～112℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.25～8.22(m, 1H), 7.86～7.83(m, 2H), 7.73～7.66(1H, m), 7.58～7.55(m, 1H), 7.45～7.40(1H, m), 7.37～7.33(2H, m), 6.83(1H, s), 2.55(3H, s)

IR(KBr): 1654, 1594, 1464, 1379, 1099㎝$^{-1}$

Step 3: 3-Iodo-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one

To a solution of 2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one(0.20g, 0.75mmol) from Step 2 in anhydrous tetrahydrofuran(THF, 15㎖) was added 2M LDA (0.38㎖, 1 equivalent) by syringe with stirring at a temperature of -78℃ for 15 minutes under Argon gas atmosphere and then iodine(0.19g, 0.75mmol) in THF(5㎖) was added. The mixture was warmed to room temperature and then stirred for 12 hours. After the reaction being complete, the reaction mixture was poured into saturated $Na_2S_2O_3$(100㎖) and stirred for 1 hour, and the mixture was extracted two times with CH_2Cl_2 (30㎖ per each) and the organic layer was washed with brine and dried over anhydrous $MgSO_4$ and filtered. The residue was subjected to flash chromatography using a mixture of hexane :ethyl acetate(7 : 1) as an eluant to afford the title compound as a pale yellow solid(0.23g, 78%).

mp: 150～152℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.30～8.27(1H, m), 7.77～7.74(2H, m), 7.73～7.70(1H, m), 7.51～7.44(2H, m), 7.38～7.35(2H, m), 2.57(3H, s)

IR(KBr): 3032, 2912, 1646, 1599, 1490, 1330, 1060, 752㎝$^{-1}$

Step 4: 3-Iodo-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

To a solution of 3-iodo-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one(0.34g, 0.86mmol) from Step 3 in MeOH(10㎖) and THF(10㎖) was added a solution of Oxone (1.59g, 2.59mmol) in H_2O(10㎖) dropwise at a temperature of 0 ℃. The resulting mixture was stirred for 3 hours. And the solution was extracted two times with CH_2Cl_2 (20㎖ per each), and the organic layer was washed with brine and dried over anhydrous $MgSO_4$. And the resulting solution was filtered and concentrated under reduced pressure. Recrystallization of the resulting residue with CH_2Cl_2 and petroleum ether yielded the title compound as a white solid(0.33g, 90%)

mp: 164~165℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.33~8.29(1H, m), 8.15~8.12(2H, m), 8.03~7.99(2H, m), 7.80~7.74(1H, m), 7.53~7.49(2H, m), 3.16(3H, s)

IR(KBr): 1643, 1470, 1301, 1151, 960, 750 cm^{-1}

Step 5: 3-(4-Fluorophenyl)-2-(4-methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

To a solution of 3-iodo-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one (0.33g, 90%) from Step 4, 4-fluorobenzeneboronic acid(0.036g, 0.26mmol) in toluene(1㎖) and EtOH(1㎖) was added 2M aqueous sodium carbonate (0.61㎖) and then tetrakis(triphenylphosphine)palladium(0.014g, 0.012mmol) and was stirred at a temperature of 90℃ for 4 hours. After being concentrated under reduced pressure, it was dissolved in dichloromethane(10㎖) and washed with water, brine. The organic layer was dried over anhydrous $MgSO_4$. And the resulting solution was filtered and concentrated under reduced pressure. The residue was subjected to flash chromatography using a mixture of hexane :ethyl acetate(1 : 1) as an eluant to yield the title compound as a pale yellow solid(0.046g,

59%).

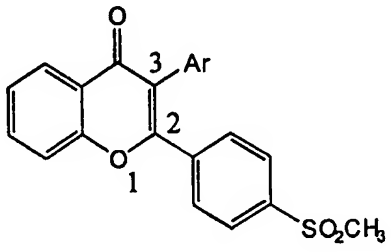
mp: 208~210℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.32~8.30(1H, m), 7.90~7.87(2H, d), 7.79~7.73(1H, m), 7.62~7.60(2H, d), 7.57~7.54(1H, d), 7.51~7.46(1H, m), 7.21~7.16(2H, m), 7.07~7.01(2H, m), 3.07(3H, s)

IR(KBr): 3017, 2922, 1640, 1509, 1468, 1378, 1290, 1230, 1155, 1142, 770 cm^{-1}

[Example 2 - 21]

The inventive compounds of Examples 2 - 21 were produced by the same procedure described in Example 1, but substituting appropriate boronic acid or boronate for 4-fluorobenzeneboronic acid in Example 1, step 5. These compounds and their physical properties are shown in Table 1.



<Table 1>

Example	3-Ar	mp (℃)	^{1}H NMR($CDCl_3$, 300MHz); δ	IR(KBr) ; cm^{-1}
2	phenyl	208-209	8.34~8.31(1H,m), 7.88~7.85(2H,m), 7.79~7.74(1H,m), 7.64~7.55(3H,m), 7.51~7.46(1H,m), 7.36~7.33(3H,m), 7.23~7.20(2H, m), 3.06(3H, s)	3020, 2923, 1621, 1467, 1378, 1295, 1152
3	4-methylphenyl	225	8.32~8.29(1H,m), 7.88~7.85(2H,d), 7.77~7.71(1H,m), 7.64~7.62(2H,d), 7.56~7.44(2H,m), 7.16~7.07(4H,m), 3.06(3H,s), 2.36(3H, s)	1644, 1377, 1297
4	3-nitrophenyl	223-224	8.33~8.30(1H,m), 8.22~8.18(1H,m), 8.10(1H,m), 7.93~7.90(2H,m), 7.83~7.77(1H,m), 7.63~7.49(6H,m), 3.06(3H,s),	3080, 2914, 1640, 1526, 1462, 1350, 1143
5	2, 4-dichlorophenyl	172-175	8.32~8.29(1H,m), 7.93~7.91(2H,m), 7.81~7.75(1H,m), 7.66~7.63(2H,m), 7.59~7.47(3H,m), 7.11~7.09(1H,d), 3.07(3H,s)	1642, 1472, 1302, 1145, 774
7	2-thienyl	165-167	8.33~8.30(1H,m), 8.15~8.12(2H,m), 8.02~7.99(2H,m), 7.95~7.93(1H,m), 7.80~7.72(2H,m), 7.55~7.46(3H,m), 3.16(3H,s)	1668, 1300, 1157
8	4-acetylphenyl	223-224	8.33~8.30(1H,m), 7.95~7.86(4H, m); 7.81~7.75(1H,m), 7.63~7.59(2H, m), 7.56(1H, s), 7.53~7.47 (1H, m), 7.36~7.32(2H, m), 3.07(3H, s), 2.62(3H, s)	1690, 1646, 1376, 1142
9	4-formylphenyl	189-190	10.03(1H, s), 8.33~8.29(1H, m), 7.90~7.84(4H,m), 7.80~7.75(1H, m), 7.63~7.60(2H,m), 7.57(1H, s), 7.53~7.48(2H, m), 7.43~7.39(2H,m), 3.07(3H, s)	2925, 1642, 1466, 1379, 1301, 1143
10	4-methoxyphenyl	212-213	8.32~8.29(1H,m), 7.89~7.86(2H, d), 7.77~7.71(1H,m), 7.65~7.62 (2H,d), 7.56~7.53(1H,d), 7.47 (1H, t), 7.14~7.11(2H, d), 6.89 ~6.86(2H, d), 3.82(3H, s), 3.06(3H, s)	3006, 2915, 1632, 1608, 1513, 1465, 1376, 1300, 1141

Example	3-Ar	mp (℃)	^{1}H NMR($CDCl_3$, 300MHz); δ	IR(KBr) ; cm^{-1}
11	3,4-dichlorophenyl	164-165	8.31 ~ 8.28(1H,m), 7.95 ~ 7.92(2H,m), 7.80 ~ 7.74(1H,m), 7.65 ~ 7.62(2H, m), 7.58 ~ 7.50(2H,m),7.41 ~ 7.37(2H, m), 7.03 ~ 7.00(1H,m), 3.08(3H, s)	1643, 1619, 1470, 1301, 1151
12	2-fluorophenyl	180-181	8.33 ~ 8.30(1H,m),7.90 ~ 7.87(2H,m),7 .79 ~ 7.74(1H m), 7.66 ~ 7.63 (2H, m), 7.58 ~ 7.46(2H, m), 7.40 ~ 7.32(1H,m), 7.24 ~ 7.20(3H, m) , 3.06(3H, s)	3089, 2931, 1640, 1469, 1376, 1300, 1142, 769
13	1-naphthyl	193-194	8.34 ~ 8.30(1H,m),7.91 ~ 7.77(3H, m),7.74 ~ 7.61(4H, m), 7.54 ~ 7.43 (5H, m), 7.44 ~ 7.36(1H, m), 7.20 ~ 7.17(1H, m), 2.96(3H, s)	2925, 1638, 1464, 1317, 1156, 764
14	2, 3-dichlorophenyl	135-137	8.32 ~ 8.29(1H,m), 7.93 ~ 7.91(2H,m), 7.81 ~ 7.75(1H,m), 7.66 ~ 7.63(2H,m), 7.59 ~ 7.47(3H,m), 7.11 ~ 7.09(1H,d), 3.07(3H,s)	1642, 1607, 1468, 1381, 1309, 1145, 772
15	3-pyridinyl	220-221	8.57 ~ 8.54(1H,m),8.33 ~ 8.29(2H,m), 7.92 ~ 7.88(2H,m),7.82 ~ 7.70 (2H, m), 7.62 ~ 7.48(4H, m), 7.37 ~ 7.34(1H,m), 3.07(3H, s)	3052, 2923, 1639, 1466, 1381, 1301, 1156, 787
16	4-pyridinyl	204-205	8.61 ~ 8.58(2H,m),8.33 ~ 8.29(1H,m), 7.93 ~ 7.89(2H, m), 7.82 ~ 7.75 (1H, m), 7.64 ~ 7.48(4H, m), 7.18 ~ 7.15(2H, m), 3.07(3H, s)	2990, 1642, 1467, 1382, 1302, 1145, 784
17	N-methyl-3-pyrazolyl	202-203	8.31 ~ 8.28(1H,m),8.01 ~ 7.98(2H,m), 7.83 ~ 7.79(3H,m),7.75 ~ 7.69(1H,m), 7.52 ~ 7.43(2H,m),6.97 ~ 6.96(1H,m), 3.91(3H,s), 3.07(3H, s)	3091,2925, 1641,1467, 1313,1154, 766
18	2-methoxy-5-pyridinyl	226-227	8.31 ~ 8.28(1H,m),7.93 ~ 7.86(3H,m), 7.79 ~ 7.73(1H,m), 7.66 ~ 7.63 (2H, m), 7.60 ~ 7.45(3H, m), 6.80 ~ 6.77(1H, m), 3.92(3H, s), 3.09(3H, s)	3054,2924, 1641,1601, 1496,1466, 1369,1301, 1144,769
19	5-bromo-3-pyridinyl	197-199	8.62 ~ 8.60(1H,m),8.31 ~ 8.28(1H,m), 8.18 ~ 8.16(1H,m),7.96 ~ 7.93(2H,m), 7.83 ~ 7.76(1H, m), 7.64 ~ 7.49(5H, m), 3.09(3H, s)	3065,2925, 1613,1466, 1378,1315, 1153,765

Example	3-Ar	mp (℃)	^{1}H NMR($CDCl_3$, 300MHz); δ	IR(KBr) ; cm^{-1}
20	2-methyl-5-pyridinyl	195-196	8.31～8.28(1H,m), 8.21～8.19(1H,m), 7.92～7.88(2H,m), 7.79～7.73 (1H, m), 7.63～7.46(5H, m), 7.21～7.18(1H, m), 3.08(3H, s), 2.57(3H, s)	2924,1641, 1466,1400, 1301,1144, 764
21	2-trifluoromethyl-5-pyridinyl	215-217	8.44～8.43(1H,m), 8.33～8.29(1H,m), 7.96～7.92(2H,m), 7.84～7.72 (2H, m), 7.63～7.50(5H, m), 3.10(3H, s)	3050,1645, 1467,1337, 1145,1088, 761

[Example 22] 3-(3-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

Step 1; 3-Bromo-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one

A solution of (4-(methylthio)phenyl)-4H-1-benzopyran-4-one(0.50g, 1.86mmol) and NBS(0.36g, 2.05mmol) in $CHCl_3$(30㎖) was heat to reflux for 5 hours. The resulting mixture was washed with saturated $NaHCO_3$, brine and dried over anhydrous $MgSO_4$, and filtered, and concentrated under reduced pressure. The residue was subjected to flash chromatography using a mixture of hexane : ethyl acetate(4 : 1) as an eluant to yield the title compound as a pale yellow solid(0.60g, 93%).

mp: 162～163℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.30～8.27(1H, m), 7.84～7.80(2H, m), 7.74～7.69(1H, m), 7.51～7.43(2H, m), 7.38～7.34(2H, m), 2.55(3H, s)

IR(KBr): 1658, 1611, 1463, 1331, 1065, 753 cm^{-1}

Step 2; 3-Bromo-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

Following the same oxidation procedure of Example 1, Step 4, but replacing 3-iodo-2 -(4-(methylthio)phenyl)-4H-1-benzopyran-4-one by 3-bromo-2-(4-(methylthio)- phenyl)-4H-1-benzopyran-4-one(0.6g, 0.86mmol) from Step 1, the

title compound was obtained as a solid(0.59g, 90%).

mp: 211~213℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.34~8.30(1H, m), 8.15~8.05(4H, m), 7.80~7.74(1H, m), 7.54~7.49(2H, m), 3.15(3H, s)

IR(KBr): 1646, 1310, 1146, 1075 cm^{-1}

Step 3; 3-(3-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

Following the procedure of Example 1, Step 5, but substituting 3-bromo-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one(0.18g, 0.47mmol) for 3-iodo-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one and *m*-tolylboronic acid(0.071g, 0.52mmol) for 4-fluorobenzeneboronic acid, the title compound was obtained as a solid(0.13g, 70%).

mp: 178~179℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.31~8.29(1H, m), 7.87~7.84(2H, m), 7.76~7.72(1H, m), 7.64~7.61(2H, m), 7.56~7.44(2H, m), 7.22~7.06(2H, m), 6.96~ 6.93(1H, m), 3.05(3H, s), 2.31(3H, s)

IR(KBr): 2920, 1639, 1465, 1377, 1299, 1149, 771 cm^{-1}

[Example 23] 3-(2-Methylphenyl)-2-(4-(methylsulfonl)phenyl)-4H-1-benzopyran-4-one

Following the procedure of Example 22, Step 3, but replacing *m*-tolylboronic acid by *o*-tolylboronic acid, the title compound was obtained as a solid.

mp: 190~191℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.32~8.29(1H, m), 7.86~7.83(2H, m), 7.79~ 7.74(1H, m), 7.60~7.57(3H, m), 7.51 ~7 .46(1H, m), 7.28~7.26(2H, m),

7.18 ~ 7.16(1H, m), 7.01 ~ 6.99(1H, m), 3.04(3H, s), 2.15(3H, s)

IR(KBr): 1618, 1376, 1324, 1156, 766 cm^{-1}

[Example 24] 3-(3-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1 -benzopyran-4-one

Following the procedure of Example 22, Step 3, but replacing *m*-tolylboronic acid by 3-chlorobenzeneboronic acid, the title compound was obtained as a solid.

mp: 195 ~ 196 ℃

^1H NMR($CDCl_3$, 300MHz): δ 8.32 ~ 8.27(1H, m), 7.91 ~ 7.89(2H, m), 7.80 ~ 7.74(1H, m), 7.64 ~ 7.61(2H, m), 7.58 ~ 7.49(2H, m), 7.31 ~ 7.28(2H, m), 7.26 ~ 7.25(1H, m), 7.07 ~ 70.5(1H, m), 3.07(3H, s)

IR(KBr): 1645, 1466, 1377, 1141 cm^{-1}

[Example 25] 3-(3-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

Following the procedure of Example 22, Step 3, but replacing *m*-tolylboronic acid by 3-fluorobenzeneboronic acid, the title compound was obtained as a solid.

mp: 225 ℃

^1H NMR($CDCl_3$, 300MHz): δ 8.36 ~ 8.33(1H, m), 7.91 ~ 7.89(2H, m), 7.80 ~ 7.73(1H, m), 7.64 ~ 7.61(2H, m), 7.58 ~ 7.46(2H, m), 7.34 ~ 7.28(2H, m), 7.08 ~ 6.97(2H, m), 3.07(3H, s)

IR(KBr): 3022, 1646, 1468, 1379, 1296, 1142, 770 cm^{-1}

[Example 26] 3-(3-Chloro-4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl) -4H-1-benzopyran-4-one

Following the procedure of Example 22, Step 3, but replacing *m*-tolylboronic acid by 3-chloro-4-fluorobenzeneboronic acid, the title compound was obtained as a solid.

mp: 196℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.32~8.25(1H, m), 7.94~7.91(2H, m), 7.80~7.75(1H, m), 7.65~7.61(2H, m), 7.58~7.47(2H, m), 7.34~7.31(1H, m), 7.13~7.01(2H, m), 3.08(3H, s)

IR(KBr): 1618, 1466, 1375, 1301, 1144, 761 cm^{-1}

[Example 27] 3-(4-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

Step 1; 3-(4-Chlorophenyl)-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one

Following the procedure of Example 1, Step 5, but substituting 3-bromo-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one(0.1g, 0.29mmol) for 3-iodo-2-(4-(methylsulfonyl)phenyl) and 4-chlorobenzeneboronic acid(0.05g, 0.32mmol) for 4-fluorobenzeneboronic acid, the title compound was obtained as a solid(0.02g, 20%).

mp: 145~147℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.30~8.26(1H, m), 7.73~7.72(1H, m), 7.55~7.44(3H, m), 7.33~7.29(3H, m), 7.20~7.12(4H, m), 2.48(3H, s)

IR(KBr): 1636, 1594, 1465, 1092 cm^{-1}

Step2;3-(4-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

Following the procedure of Example 1, Step 4, but replacing 3-iodo-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one by 3-(4-chlorophenyl)-2-(4-

(methylthio)phenyl)-4H-1-benzopyran-4-one(0.05g, 0.12mmol), the title compound was obtained as a solid(0.048g, 89%).

mp: 187~188℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.32~8.28(1H, m), 7.91~7.89(2H, m), 7.79~7.73(1H, m), 7.63~7.61(2H, m), 7.57~7.46(2H, m), 7.34~7.27(2H, m), 7.17~7.14(2H, m), 3.08(3H, s)

IR(KBr): 3083, 2926, 1617, 1465, 1377, 1301, 1157, 1091, 770 cm^{-1}

[Example 28] 3-(4-Bromophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

Following the same oxidation procedure of Example 1, Step 4, but replacing 3-iodo-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one by 3-(4-bromophenyl)-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one (0.06g, 0.14mmol), the title compound was obtained as a solid(0.059g, 90%).

mp: 168~170℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.32~8.28(1H, m), 7.92~7.89(2H, m), 7.77~7.73(1H, m), 7.63~7.46(6H, m), 7.11~7.08(2H, m), 3.08(3H, s)

IR(KBr): 3027, 2925, 1640, 1465, 1375, 1300, 1142, 772 cm^{-1}

[Example 29] 2-(4-(Methylthio)phenyl)-3-(4-trifluoromethylphenyl)-4H-1-benzopyran-4-one

Following the procedure of Example 1, Step 5, but substituting 3-bromo-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one(0.1g, 0.32mmol) for 3-iodo-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one and 4-trifluoromethylbenzeneboronic acid(0.066g, 0.35mmol) for 4-fluorobenzeneboronic acid, the title compound was obtained as a solid(0.05g, 40%).

mp: 189~192℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.31~8.27(1H, m), 7.77~7.70(1H, m), 7.61~7.54(3H, m), 7.49~7.43(1H, m), 7.39~7.36(2H, m), 7.31~7.28(2H, m), 7.15~7.11(2H, m), 2.48(3H, s)

IR(KBr): 2870, 1663, 1425, 1295, 1010 cm^{-1}

[Example 30] 2-(4-(Methylsulfonyl)phenyl)-3-(4-trifluoromethylphenyl)-4H-1-benzopyran-4-one

Following the same oxidation procedure of Example 1, Step 4, but replacing 3-iodo-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one by 2-(4-(methylthio) phenyl)-3-(4-trifluoromethylphenyl)-4H-1-benzopyran-4-one(0.027g,0.065mmol), the title compound was obtained as a solid(0.03g, 100%).

mp: 213~216℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.33~8.29(1H, m), 7.92~7.88(2H, m), 7.81~7.75(1H, m), 7.63~7.47(6H, m), 7.37~7.34(2H, m), 3.08(3H, s)

IR(KBr): 2927, 1641, 1455, 1378, 1325, 1143, 1109, 1017, 771 cm^{-1}

[Example31] 3-(3,5-Dichlorophenyl)-2-(4-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

Step 1; 3-(3,5-Dichlorophenyl)-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one

Following the procedure of Example 1, Step 5, but substituting 3,5-dichlorobenzeneboronic acid(0.067g, 0.35mmol) for 4-fluorobenzeneboronic acid and 3-bromo-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one(0.1g, 0.29mmol) for 3-iodo-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one, the title compound was obtained as a solid(0.043g, 36%).

mp: 198~200℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.29~8.25(1H, m), 7.77~7.70(1H, m), 7.57~7.43(2H, m), 7.35~7.14(5H, m), 6.94~6.92(1H, m), 6.75~6.74(1H, m), 2.50(3H, s)

IR(KBr): 2880, 1650, 1430, 1253, 950 cm^{-1}

Step 2 ; 3-(3,5-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzo-pyran-4-one

Following the same oxidation procedure of Example 1, Step 4, but replacing 3-iodo-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one by 3-(3,5-dichloro-phenyl)-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one(0.04g, 0.096mmol), the title compound was obtained as a solid(0.02g, 47%).

mp: 258~260℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.32~8.28(1H, m), 7.97~7.93(2H, m), 7.81~7.75(1H, m), 7.66~7.62(2H, m), 7.59~7.48(2H, m), 7.35~7.33(1H, m), 7.11~7.10(2H, m), 3.08(3H, s)

IR(KBr): 3011, 2920, 1628, 1580, 1453, 1373, 1305, 1299, 1155, 961, 764 cm^{-1}

[Example 32] 3-(2-Chloro-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one and 3-(4-Chloro-3-pyridinyl)-2-(4-(methylsulfonyl)-phenyl)-4H-1-benzopyran-4-one

Step 1 ; 2-(4-(Methylsulfonyl)phenyl)-3-(N-oxo-3-pyridinyl)-4H-1-benzopyran-4-one

A solution of 2-(4-(methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-one(0.2g, 0.54mmol) from Example 15 and MCPBA(0.18g, 0.6mmol) in CH_2Cl_2(20mL) was refluxed for 1.5 hours. Then the mixture was

cooled to room temperature and washed with 1N NaOH solution. The organic layer was dried and concentrated *in vacuo* to yield the title compound as a pale yellow solid(0.2g).

mp: 231-232℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.32~8.28(1H, m), 8.18~8.15(1H, m),8.04~8.03(1H, m), 7.99~7.95(2H, m), 7.83~7.76(1H, m), 7.69~7.65(2H, m), 7.60~7.50(2H, m), 7.33~7.21(2H, m), 3.11(3H, s)

IR(KBr): 2923,1641,1467,1385, 1303,1261,1144,760 cm^{-1}

Step 2 ;

compound A; 3-(2-Chloro-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

compoundB;3-(4-Chloro-3-pyridinyl)-2-(4-(methylsulfonyl)-phenyl)-4H-1-benzopyran-4-one

A solution of 2-(4-(methylsulfonyl)phenyl)-3-(N-oxo-3-pyridinyl)-4H-1-benzopyran-4-one(0.2g, 0.51mmol) in $POCl_3$(2mL) was heated at a temperature of 110 ℃ for 6.5 hours. After evaporating the excess $POCl_3$, the residue was poured into ice and made alkaline with NH_4OH and extracted with CH_2Cl_2. After the solvent being evaporated, the residue was subjected to flash chromatography to yield the title compound as a pale yellow solid(A; 0.092g, B; 0.03g).

compound A;

mp: 232-233℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.31~8.28(1H, m), 8.14~8.06(2H, m), 7.96~7.93(2H, m), 7.82~7.75(1H, m), 7.73~7.69(1H, m), 7.64~7.48(4H, m), 7.42~7.36(1H, m), 3.09(3H, s)

IR(KBr): 2920,1647,1465,1308,1140,760 cm^{-1}

compound B;

mp: 235-236℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.51~8.49(1H, m), 8.33~8.29(2H, m), 7.92~7.89(2H, m), 7.83~7.76(1H, m), 7.63~7.42(5H, m), 3.06(3H, s)

IR(KBr): 2925,1643,1466,1307,1145,767 cm^{-1}

[Example 33] 2-(4-(Methylsulfonyl)phenyl)-3-(2-pyridinyl)-4H-1 -benzopyran-4-one

A solution of 3-bromo-2-(4-(methylsulfonyl)phenyl)-4H-1 -benzopyran-4 -one (0.5g, 1.32mmol) from Example 22, Step 2 and 2-tributylstannylpyridine(0.58g, 1.58mmol) and tetrakis(triphenylphosphine)palladium(0.15g, 0.13mmol) in N-methyl-2-pyrrolidine(50mℓ) and ethanol(1mℓ) was heated at a temperature of 100℃ for 24 hours. Then the mixture was cooled to room temperature and diluted with ethyl acetate and filtered through a pad of celite. The mixture was washed with 5% aqueous KF, dried and concentrated. The residue was subjected to flash chromatography to yield the title compound as a pale yellow solid(0.27g).

mp: 203~204℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.55~8.52(1H, m), 8.33~8.29(1H, m),7.88~7.84(2H, m), 7.79~7.73(2H, m), 7.60~7.55(3H, m), 7.51~7.46(2H, m), 7.29~7.24(1H, m), 3.05(3H, s)

IR(KBr): 3058, 1642, 1467, 1382, 1303, 1146, 769 cm^{-1}

[Example34]6-Fluoro-2-(4-(methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-one

Step 1; 5'-Fluoro-2'-hydroxy-4-(methylthio)chalcone

The title compound was prepared from 4-(methylthio)benzaldehyde and 5'-

fluoro-2'-hydroxyacetophenone by the same method as described in Step 1 of Example 1.

mp: 147~148℃

^{1}H NMR($CDCl_3$, 300MHz): δ 7.92(1H, d, J=15.6Hz), 7.61~7.57(3H, m), 7.50(2H, d, J=15.3Hz), 7.30~7.21(2H, m), 7.03~6.98(1H, m), 2.54(3H, s)

IR(neat): 1640, 1573, 1482, 1359, 1170, 1097, 776 cm^{-1}

Step 2 ; 6-Fluoro-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one

The title compound was prepared from 5'-fluoro-2'-hydroxy-4-(methylthio)chcalcone and iodine by the same method as described in Step 2 of Example 1.

mp: 177~178℃

^{1}H NMR($CDCl_3$, 300MHz): δ 7.88~7.81(3H, m), 7.59~7.55(1H, m), 7.45~7.39(1H, m), 7.37~7.33(2H, m), 6.78(1H, s), 2.55(3H, s)

IR(neat): 1639, 1579, 1261,818 cm^{-1}

Step 3; 6-Fluoro-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

The title compound was prepared from 6-fluoro-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one by the same method as described in Step 4 of Example 1.

^{1}H NMR($CDCl_3$, 300MHz): δ 8.16~8.08(4H, m), 7.91~7.87(1H, m), 7.65~7.60(1H, m), 7.51~7.44(1H, m), 6.89(1H, s), 3.12(3H, s)

Step 4: 6-Fluoro-3-iodo-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran -4-one

A solution of 6-fluoro-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one(3.5g, 11mmol) , iodine(2.8g, 11mmol) and [bis(trifluoroacetoxy)iodo]-benzene (3.5g, 11mmol) in CH_2Cl_2(250㎖) was stirred at room temperature for 24

hours. The resulting mixture was washed with saturated $Na_2S_2O_3$(100㎖), saturated $NaHCO_3$(100㎖) and then washed with brine and dried over anhydrous $MgSO_4$ and concentrated. Recrystallization of the resulting residue by CH_2Cl_2 and petroleum ether yielded the title compound as a white solid(2.5g, 71%).

^1H NMR($CDCl_3$, 300MHz): δ 8.14~8.10(2H, m), 8.01~7.91(3H, m),7.55~7.44(2H, m), 3.15(3H, s)

Step 5: 6-Fluoro-2-(4-(methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1 -benzopyran-4-one

The title compound was prepared from 6-fluoro-3-iodo-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one and lithium trimethoxy-3-pyridinylboronate by the same method as described in Step 5 of Example 1.

mp: 233~234℃

^1H NMR($CDCl_3$, 300MHz): δ 8.60~8.54(1H, m), 8.36~8.28(1H, m), 7.96~7.88(3H, m), 7.77~7.73(1H, m), 7.62~7.47(4H, m), 7.40~7.34(1H, m), 3.07(3H, s)

IR(neat): 2928, 1642, 1483, 1272, 1152, 766 cm^{-1}

[Example 35] 6-Fluoro-3-(2-methyl-5-pyridinyl)-2-(4-(methylsulfonyl) -phenyl)-4H-1-benzopyran-4-one

Following the procedure of Example 34, Step 5, but substituting lithium trimethoxy-2-methyl-5-pyridinylboronate for lithium trimethoxy-3-pyridinylboronate, the title compound was obtained as a solid.

mp: 145-148℃

^1H NMR($CDCl_3$, 300MHz): δ 8.20~8.19(1H, m), 7.95~7.89(3H, m),7.63~7.45(5H, m), 7.23~7.20(1H, m), 3.08(3H, s), 2.58(3H, s)

IR(KBr): 2925,1613,1451,1315,1150,767 cm^{-1}

[Example 36] 3-(4-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione

A solution of 3-(4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one(0.45g, 1.14mmol) from Example 1 and Lawesson's reagent(0.23g, 0.57mmol) in toluene(10㎖) was refluxed for 1 hour. The resulting mixture was concentrated and subjected to flash chromatography using a mixture of hexane :ethyl acetate: dichloroethane(1 : 1 :1) as an eluant to yield the title compound as a deep green solid(0.4g, 85%).

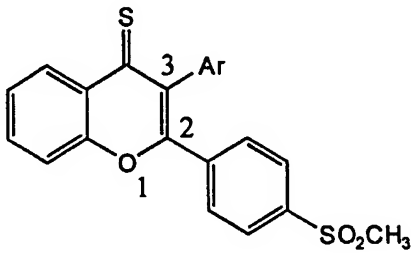
mp: 203～205℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.67～8.64(1H, m), 7.88～7.85(2H, d), 7.80～7.75(1H,m), 7.60～7.57(2H, d), 7.55(1H, s), 7.51～7.46(1H, m), 7.16～7.02(4H, m), 3.06(3H, s)

IR(KBr): 2929, 1605, 1589, 1536, 1508, 1459, 1400, 1377, 1314, 1297, 1254, 1151, 833 cm^{-1}

[Example 37 - 46]

The inventive compounds of Examples 37 - 46 were produced by the same procedure described in Example 36, but substituting appropriate benzopyranone for 3-(4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one. These compounds and their physical properties are shown in Table 2.



<Table 2>

Example	3-Ar	mp (℃)	^{1}H NMR($CDCl_3$, 300MHz); δ	IR(KBr) ; cm^{-1}
37	phenyl	204-206	8.68~8.65(1H,m),7.84~7.81(2H,d), 7.80~7.74(1H,m), 7.60~7.58 (2H,d), 7.55(1H,s),7.50~7.45(1H,m), 7.36~7.34(3H, m), 7.18~7.15(2H,m), 3.04(3H, s)	2931, 1589, 1455, 1375, 1298, 1150
38	2, 3-dichlorophenyl	191-192	8.65~8.63(1H,m),7.91~7.89(2H,m), 7.82~7.76(1H,m),7.67~7.64(2H,m), 7.59~7.56(1H,m),7.52~7.46(2H,m), 7.22~7.16(1H, m), 7.05~7.02(1H,m), 3.06(3H, s)	1594, 1542, 1457, 1296, 1152
39	3-methylphenyl	201-202	8.68~8.64(1H,m),7.85~7.82(2H,m), 7.57~7.54(1H,m),7.49~7.44(1H,m), 7.26~7.16(2H,m), 6.97~ 6.94(2H,m), 3.04(3H,s), 2.30(3H, s)	1607, 1539, 1458, 1374, 1299, 1264, 1152
40	3-chlorophenyl	196-198	8.64~8.61(1H,m),7.88~7.85(2H,m), 7.77~7.74(1H,m),7.61~7.55(3H,m), 7.50~7.45(1H,m),7.34~7.24(2H,m), 7.17~7.16(1H, m), 7.06~7.03(1H,m), 3.05(3H, s)	1589, 1249, 1152
41	2-methylphenyl	234	8.68~8.64(1H,m),7.85~7.82(2H,m), 7.81~7.78(1H,m),7.61~7.58(2H,m), 7.51~7.48(1H, m), 7.33~7.16(4H,m), 7.01~ 6.99(1H, m), 3.04(3H, s), 2.08(3H, s)	2913, 1590, 1541, 1458, 1298, 1253, 1150
42	3, 4-dichlorophenyl	168	8.65~8.60(1H,m),7.93~7.90(2H,m), 7.82~7.76(1H,m), 7.63~7.60 (2H, m), 7.58~7.41(3H, m), 7.28(1H, d), 7.03~6.99(1H, m), 3.07(3H, s)	1591, 1463, 1319, 1243, 1153, 774
43	4-methylphenyl	204-205	8.68~8.64(1H,m),7.84~7.82(2H,d), 7.78~7.73(1H,m),7.61~7.59(2H,d), 7.57~7.44(2H,m),7.17~7.15(2H,d) ,7.05~7.02(2H, d), 3.05(3H, s), 2.37(3H, s)	2918, 1593, 1370, 1298, 1251, 1149
44	4-methoxyphenyl	199	8.68~8.65(1H,d),7.86~7.83(2H,d), 7.78~7.72(1H,m),7.62~7.59(2H,d), 7.56~7.44(2H, m),7.09~7.06(2H,d), 6.89~6.87(2H, d), 3.83(3H, s), 3.05(3H, s)	1590, 1510, 1459, 1297, 1152

Example	3-Ar	mp (℃)	^{1}H NMR($CDCl_3$, 300MHz); δ	IR(KBr) ; cm^{-1}
45	2-fluorophenyl	198- 200	8.67～8.64(1H,d),7.88～7.85(2H,d), 7.80～7.75(1H,m), 7.66～7.63(2H,d), 7.57～7.55(1H,d), 7.50～ 7.45(1H,t), 7.36(1H, m), 7.14～ 7.06(3H, m), 3.05(3H, s)	3088, 1591, 1537, 1465, 1460, 1376, 1152, 757
46	3-fluorophenyl	212	8.65～8.63(1H,m), 7.87～7.85(2H, m), 7.80～7.74(1H, m), 7.63～7.55 (3H, m), 7.50～7.45(1H, m), 7.36 ～7.28(1H, m), 7.08～7.02(1H, m), 6.96～6.89(2H, m), 3.05(3H, s)	3032, 1591, 1297, 1261, 1127

[Example 47] 2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-phenyl-4H-1-benzopyran-4-one

Step1:3-Bromo-6-fluoro-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one

A solution of 6-fluoro-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one(7.43g, 25.95mmol) from Example 34, Step 2 and NBS(6.93g, 38.93mmol) in $CHCl_3$(100㎖) was refluxed for 20 hours. The resulting mixture was washed with saturated $NaHCO_3$, brine and dried over anhydrous $MgSO_4$. Recrystallization of the resulting residue by CH_2Cl_2 and petroleum ether yielded the title compound as a solid(7.38g, 78%).

mp: 228～229℃

^{1}H NMR($CDCl_3$, 300MHz): δ 7.93(1H. dd, J=7.8, 3.0Hz), 7.84～7.79(2H, m), 7.5～7.50(1H, m), 7.48～7.41(1H, m), 7.39～7.34(2H, m), 2.56(3H, s)

IR(KBr): 1651, 1477, 1261, 1062, 823cm^{-1}

Step 2: 3-Bromo-6-fluoro-2-(4-(methylsulfinyl)phenyl)-4H-1-benzopyran-4-one

To a solution of 3-bromo-6-fluoro-2-(4-(methylthio)phenyl)-4H-1 -

benzopyran-4-one(7.3g, 19.9mmol) from Step 1 in CH_2Cl_2(700㎖) was added a solution of MCPBA(4.0g, 19.9mmol) in CH_2Cl_2(200㎖) at a temperature of 0℃ for 2 hours. The solution was washed two times with saturated Na_2CO_3(100㎖ per each) and the organic layer was washed with H_2O, brine and dried over anhydrous $MgSO_4$. After the solvent being evaporated, the resulting solid was subjected to flash chromatography using a mixture of ethyl acetate : CH_2Cl_2(1 : 1) as an eluant to yield the title compound as a solid(6.1g, 80%) .

mp: 172～174℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.05～8.01(2H, m), 7.96～7.93(1H, m), 7.86～7.82(2H, m), 7.57～7.44(2H, m), 2.83(3H, s)

IR(neat): 2988, 1657, 1481, 1275, 1261, 1081㎝$^{-1}$

Step 3; 2-(4-(Aminosulfonyl)phenyl)-3-bromo-6-fluoro-4H-1-benzopyran-4-one

A solution of 3-bromo-6-fluoro-2-(4-(methylsulfinyl)phenyl)-4H-1-benzopyran-4-one(6.17g, 16.18mmol) in TFAA(trifluoroacetic anhydride, 100㎖) was refluxed for 2 hours. The solvent was removed and the resulting residue was coevaporated three times with using a triethylamine/MeOH solution(50㎖, 1:1) to yield oil. The oil was dissolved in AcOH(100㎖) and treated at room temperature with Cl_2 in AcOH(50㎖). After stirring for 2 hours, the solvent was removed and THF(100㎖) was added to the resulting product. After excessive amount of NH_4OH solution was added at a temperature of 0℃, the reaction mixture was stirred for 2 hours at room temperature. Water was added and the product was extracted two times with ethyl acetate(100㎖ per each). The extract was dried over anhydride $MgSO_4$ and concentrated. Recrystallization of the resulting residue by CH_2Cl_2 and petroleum ether yielded the title compound as a solid(3.83g, 60%).

mp: 266～267℃

^{1}H NMR($CDCl_3$-MeOH-d_4, 300MHz): δ 8.12~8.10(2H, m), 8.02~7.99(2H, m), 7.92(1H, dd, J=8.1, 3.0Hz), 7.64~7.51(2H, m)

IR(KBr): 3300, 3236, 1647, 1552, 1481, 1333, 1163, 1081, 755 cm^{-1}

Step 4 : 2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-phenyl-4H-1-benzopyran-4-one

Following the procedure of Example 1, Step 5, but substituting benzeneboronic acid(0.056g, 0.459mmol) for 4-fluorobenzeneboronic acid and 2-(4-(aminosulfonyl)phenyl)-3-bromo-6-fluoro-4H-1-benzopyran-4-one(0.153g, 0.38mmol) for 3-iodo-2-(4-(methylsulfonyl)-phenyl)-4H-1-benzopyran-4-one, the title compound was obtained as a solid(0.08g, 53%).

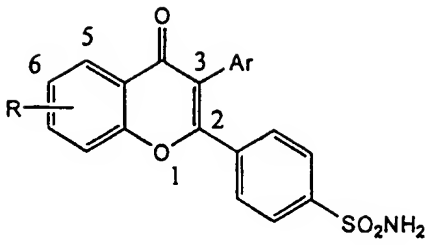
mp: 265~267℃

^{1}H NMR(DMSO-d_6, 300MHz): δ 8.22~8.19(2H, m), 7.96~7.94(2H, m), 7.82 ~ 7.75(1H, m), 7,60(1H, d, J=8.4Hz), 7.54(2H, bs, NH_2), 7.46(1H, m), 7.32~7.19(5H, m)

IR(KBr): 3358, 3268, 3069, 2924, 1691, 1481, 1306, 1164, 750 cm^{-1}

[Example 48 - 58]

The inventive compounds of Examples 48 - 58 were produced by the same procedure described in Example 47, step 4, but substituting appropriate boronic acid or boronate for benzeneboronic acid and in case of Example 52 - 58, the requisite starting material, 2-(4-(aminosulfonyl)phenyl)-3-bromo-4H-1-benzopyran-4-one was prepared in the same way to 6-fluoro analog from 2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one. These compounds and their physical properties are shown in Table 3.



<Table 3 >

Example	3-Ar	6-R	mp (℃)	^{1}H NMR(300MHz); δ	IR(KBr) ; cm^{-1}
48	4-fluorophenyl	F	224-226	(DMSO-d_6); 7.93(1H,dd,J=8.1,3.0Hz), 7.88~7.85(2H,m),7.59~7.48(4H,m), 7.20~7.16(2H,m),7.07~7.01(2H,m), 4.86(2H, bs, NH_2)	3408, 3226, 3083, 1631, 1484, 1166, 768
49	4-methylphenyl	F	215-217	($CDCl_3$); 7.91(1H,dd,J=8,1,3.0Hz), 7.84 ~7.81(2H,m),7.58~7.53(3H, m), 7.49~7.45(1H,m), 7.15~7.12 (2H, m), 7.07~7.05(2H, m), 4.99(2H, bs, NH_2)	3240, 3075, 2924, 1629, 1482, 1343, 1185, 729
50	4-chlorophenyl	F	215-217	($CDCl_3$); 7.92(1H,dd,J=8,4,3.0Hz), 7.89~7.85(2H, m), 7.60~7.45(4H,m), 7.34~7.30(2H,m),7.16~7.13(2H, m), 4.93(2H, bs, NH_2)	3386, 1629, 1481, 1343, 1185, 1095, 775
51	3-fluorophenyl	F	257-258	($CDCl_3$);7.92(1H,dd,J=8,1,3.0Hz), 7.61~7.49(4H,m) 7.09~7.02(1H,m) , 6.97~6.93 (2H,m), 4.86(2H, bs, NH_2)	3413, 3334, 3229, 1638, 1485, 1335, 1273, 1166, 764
52	4-fluorophenyl	H	267- 268	($CDCl_3$/MeOH-d_4);8.27(1H,dd,J= 8.4,1.8Hz), 7.88~ 7.77(3H,s), 7.62 ~7.48(4H, m), 7.22~7.17 (2H,m), 7.07~7.01(2H,m)	3331, 3219, 1627, 1470, 1338, 1116, 834
53	phenyl	H	218-220	($CDCl_3$/MeOH-d_4); 8.32~ 8.29(1H,m), 7.83 ~7.80(2H,m), 7.75 ~7.71(3H,m), 7.57~7.43 (2H,m), 7.34~7.32(3H,m),7.21~7.18 (2H, m), 4.86(2H, bs, NH_2)	3302, 2929, 1631, 1468, 1344, 1146, 768

Example	3-Ar	6-R	mp (℃)	^{1}H NMR(300MHz); δ	IR(KBr) ; cm^{-1}
54	3, 4-methylenedioxy	H	225-228	(DMSO-d_6);8.14～8.11(1H,m) ,7.90～7.52(7H,m), 7.46(2H,brs), 6.85 ～ 6.82 (2H,m), 6.58(1H,m), 6.03(2H,s)	3387, 2931, 1615, 1486, 1340,1243, 1168,1037, 768
55	4-methoxyphenyl	H	252-254	(DMSO-d_6);8.14～8.11(1H,m), 7.89～7.51(7H, m), 7.45(2H,brs), 7.13～ 7.10 (2H, m), 6.90～6.87(2H, m), 3.75(3H,s)	3315, 3224, 2929, 1600, 1466, 1350, 1238,1150, 768
56	4-methylthiophenyl	H	224-226	(DMSO-d_6); 8.14～8.11(1H,m), 7.92～7.52(7H, m), 7.47(2H,brs), 7.21～ 7.12 (4H, m), 2.50(3H,s)	3333, 2931, 1609, 1467, 1353, 1168, 730
57	3,4-dichlorophenyl	H	215-217	(DMSO-d_6); 8.16～8.12(1H,m), 7.94～7.40(4H, m), 7.68～7.64(2H, m), 7.60～7.54(3H, m),7.16～7.12 (1H, m), 7.47(2H,brs)	3302, 2929, 1631, 1468, 1344, 1146, 768
58	2-fluorophenyl	H	215-217	(DMSO-d_6); 8.15～8.11(1H,m), 7.92 ～7.88(1H, m), 7.81～7.55(6H, m) ,7.48(2H,brs), 7.42～7.36(1H, m), 7.27～7.14 (3H, m)	3317, 3203, 1615, 1432, 1320, 1113, 760

[Example 59] 2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(4-fluorophenyl)-4H-1-benzopyran-4-one

Step 1; 7-Fluoro-3-(4-fluorophenyl)-2-(4-(methylsulfinyl)phenyl)-4H-1-benzopyran-4-one

Following the procedure of Example 1, Step 5, but replacing 3-iodo-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one by of 3-bromo-7-fluoro-2-(4-(methylsulfinyl)phenyl)-4H-1-benzopyran-4-one(0.3g, 0.79mmol) prepared from 7-fluoro-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one in an analogous way to 6-fluoro analog of Step 1, and Step 2 in Example 47 , the title compound was obtained(0.26g, 82%).

^{1}H NMR($CDCl_3$, 300MHz): δ 8.33～8.30(1H, m), 7.70～7.63(2H, m), 7.50～7.43(2H, m), 7.61(1H, brs), 7.28～7.25(1H, m), 7.23～7.16(2H, m), 7.05～6.99(2H, m), 2.73(3H, s)

Step 2: 2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(4-fluorophenyl)-4H-1-benzopyran-4-one

Following the procedure of Example 47, Step 3, but substituting 7-fluoro-3-(4-fluorophenyl)-2-(4-(methylsulfinyl)phenyl)-4H-1-benzopyran-4-one(0.18g, 0.454mmol)for3-bromo-6-fluoro-2-(4-(methyl-sulfinyl)phenyl)-4H-1-benzopyran-4-one, the title compound was obtained as a solid(0.07g, 37%).

mp: 214～215℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.34～8.29(1H, m), 7.88～7.85(2H, m), 7.55～7.52(2H, m), 7.25～7.15(4H, m), 7.07～7.01(2H, m), 4.94(2H, s)

[Example 60] 2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(2-fluorophenyl)-4H-1-benzopyran-4-one

The title compound was prepared from 7-fluoro-3-(2-fluorophenyl) -2-(4-(methylsulfinyl)phenyl)-4H-1-benzopyran-4-one according to the procedure described in Example 59, Step 2.

mp: 188℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.34～8.29(1H, m), 7.87～7.85(2H, m), 7.59～7.56(2H, m), 7.40～7.32(1H, m), 7.25～7.02(5H, m), 4.96(2H, s)

[Example 61] 2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(3-fluorophenyl)-4H-1-benzopyran-4-one

The title compound was prepared from 7-fluoro-3-(3-fluorophenyl) -2-(4-(methylsulfinyl)phenyl)-4H-1-benzopyran-4-one according to the procedure

described in Example 59, Step 2.

mp: 239~240℃

^{1}H NMR(DMSO-d_6, 300MHz): δ 8.26~8.21(1H, m), 7.85~7.82(2H, m), 7.58~7.55(2H, m), 7.47~7.44(1H, m), 7.38(2H, s), 7.36~7.28(2H, m), 7.11~6.97(3H, m)

[Example 62] 2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(3,4-dichlorophenyl)-4H-1-benzopyran-4-one

The title compound was prepared from 7-fluoro -3-(3,4-dichlorophenyl) -2-(4-(methylsulfinyl)phenyl)-4H-1-benzopyran-4-one according to the procedure described in Example 59, Step 2.

mp: 190~191℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.33~8.28(1H, m), 7.91~7.89(2H, m), 7.57~7.54(2H, m), 7.41~7.37(2H, m), 7.23~7.19(2H, m), 7.00~6.97(1H, m), 4.98(2H, s)

[Example 63] 2-(4-Aminosulfonyl)phenyl-6-methoxy-3-(4-fluorophenyl)-4H-1-benzopyran-4-one

The title compound was prepared from 2-(4-aminosulfonyl)phenyl-3-bromo -6-methoxy-4H-1-benzopyran-4-one according to the procedure described in Example 47, Step 4.

^{1}H NMR($CDCl_3$, 300MHz): δ 7.87(2H, m), 7.54~7.53(2H, m),7.51~7.37(2H, m),7.22~7.00(5H, m), 4.90(2H, s), 4.01(3H, s)

[Example 64] 2-(4-(Aminosulfonyl)phenyl)-7-methoxy-3-(4-fluorophenyl)-4H-1-benzopyran-4-one

The title compound was prepared from 2-(4-(aminosulfonyl) -phenyl)-3-

bromo-7-methoxy-4H-1-benzopyran-4-one according to the procedure described in Example 47, Step 4.

mp: 245℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.21~8.18(1H, m), 7.87~7.85(2H, m), 7.62~7.60(2H, m),7.22~7.05(6H, m),4.87(2H, s), 4.09(3H, s)

[Example 65] 2-(4-(Aminosulfonyl)phenyl)-8-chloro-3-(4-fluorophenyl) -5-methoxy-4H-1-benzopyran-4-one

The title compound was prepared from 2-(4-(aminosulfonyl)phenyl) -3-bromo-8-chloro-5-methoxy-4H-1-benzopyran-4-one according to the procedure described in Example 47, Step 4.

mp: 279~281℃

^{1}H NMR(DMSO-d_6, 300MHz): δ 7.96(1H, dd, J=9.0, 1.2Hz), 7.79~7.76(2H, m), 7.59~7.42(3H, m), 7.46(2H, bs, NH2), 7.25~7.14(4H, m), 3.84(3H, s)

IR(KBr): 3290, 3220, 1627, 1467, 1416, 1320, 1226, 1162, 1037, 815 cm^{-1}

[Example66]2-(4-(Aminosulfonyl)phenyl)-8-chloro-3-(4-fluorophenyl)-5-hydroxy-4H-1-benzopyran-4-one

To a solution of 2-(4-(aminosulfonyl)phenyl)-8-chloro-3-(4-fluorophenyl)-5-methoxy-4H-1-benzopyran-4-one(0.03g, 0.07mmol) in CH_2Cl_2(5㎖) was added 1.0M BBr_3(0.2㎖) at a temperature of 0℃. The mixture was stirred for 4 hours at room temperature and diluted with CH_2Cl_2(10㎖). After being washed with water and brine, the solution was dried over anhydrous $MgSO_4$. The crude product was purified by flash chromatography to yield the title compound as a solid(0.02g, 74%).

mp: 251~252℃

^{1}H NMR(DMSO-d_6, 300MHz): δ 7.93(1H, d, J=9.3Hz), 7.81~7.78(2H, m), 7.62~7.60(2H, m), 7.48(2H, bs, NH_2), 7.32~7.18(5H, m)

IR(KBr): 3311, 3234, 1639,, 1592, 1434, 1223, 1167, 712cm^{-1}

[Example67]2-(4-(Aminosulfonyl)phenyl)-6-hydroxy-3-(4-fluorophenyl)-4H-1-benzopyran-4-one

The title compound was prepared from 2-(4-(aminosulfonyl)phenyl)-6-methoxy-3-(4-fluorophenyl)-4H-1-benzopyran-4-one according to the procedure described in Example 66.

^{1}H NMR($CDCl_3$, 300MHz): δ 7.88~7.84(2H, m), 7.73~7.70(2H, m),7.60~7.51(3H, m),7.45(1H, s),7.21~7.16(2H, m),7.09~7.02(2H, m), 4.92(2H, s)

[Example 68] 2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(4-fluorophenyl)-4H-1-benzopyran-4-thione

The title compound was prepared from 2-(4-(aminosulfonyl)phenyl) -6-fluoro-3-(4-fluorophenyl)-4H-1-benzopyran-4-one according to the procedure described in Example 36.

mp: 224~225℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.32(1H, dd, J=8,4, 3.0Hz), 7.85~7.82(2H, m), 7.82~7.47(4H, m), 7.15~7.11(2H, m), 7.08~7.02(2H, m), 5.30(2H, bs, NH_2)

IR(KBr): 3370, 3278, 1597, 1493, 1342, 1258, 1159, 1086, 768cm^{-1}

[Example 69] 2-(4-(Aminosulfonyl)phenyl)-3-(4-fluorophenyl)-4H-1-benzopyran-4-thione

The title compound was prepared from 2-(4-(aminosulfonyl)phenyl) -3-(4-fluorophenyl)-4H-1-benzopyran-4-one according to the procedure described in Example 36.

mp: 197~199℃

^{1}H NMR($CDCl_3$-MeOH-d_4, 300MHz): δ 8.67~8.63(1H, m), 7.84~7.75(3H, m), 7.59~7.46(5H, m), 7.16~7.12(2H, m), 7.06~7.01(2H, m)

IR(KBr): 3265, 1590, 1536, 1339, 1250, 1154, 1069, 832 cm^{-1}

[Experimental example 1]

Regarding the compounds in the above Examples and indomethacin, the inhibition efficacy of COX-2 and COX-1 are being measured by the following two methods. And the results of the inhibition efficacy of COX-2 and COX-1 are shown in Table 4.

1. Evaluation of COX-2's inhibition efficacy(J. Pharmacol.Exp.Ther.166,96(1969))

After cleaning C57BL/6 mouse's abdomen by 70% EtOH, the skin of mouse's abdomen was eliminated cautiously not to harm peritomeum and 5㎖ of cold PBS was poured into the abdominal cavity and in certain times later macrophage-bleeding abdominal-liquid was collected by syringe. By adding RPMI-1640 badge containing penicillin(100unit/㎖) and streptomycin(100 mg/㎖) to cell pellet obtained by centrifugation of collected liquid about 5 minutes in 1500 rpm, it was disperesed and also COX-1 existing in the cell was inactivated by treating with 500 μM aspirin. After putting 1㎖ cell suspension having cell number of 1×10^6cells/㎖ into each 24-well microtiter plates, macrophages were adhered to the bottom of plate by culturing in the condition of 5% CO_2/95% O_2, at a temperature of 37℃ for 2 hours. Other cells not being adhered to were eliminated by washing two times with PBS. The purity of macrophages obtained through this process was identified by differential counting. After adding RPMI-1640 badge(normally 5×10^5 cell/㎖) containing 3% right fetal blood serum to macrophage and treating it with LPS(lipopolysaccharide) to make final

concentration as 10㎍/㎖, it was cultured in the condition of 5% CO_2, at a temperature of 37℃ for 16 hours. After inducing COX-2 by LPS, the cell culture medium was eliminated and macrophages was washed two times with PBS. And 1㎖ of RRPI-1640 badge was added to each well again and after treating them with sample with appropriate concentration, they were cultured at a temperature of 37¡É for 10 minutes. And then treated them with arachidonic acid to make their final concentration as 10 μM and cultured them additional 10 minutes, all the supernatant liquid of reaction was obtained. The amount of PGE_2 produced in the supernatant liquid of reaction was determined by the PGE_2 radioimmuno assay. The 100% COX-2's activation is referenced by the difference of the amount of PGE_2 produced in the supernatant liquid of reaction between with 10 μM arachidonic acid treatment and without 10 μM arachidonic acid treatment.

2. Evaluation of COX-1's inhibition efficacy

Following the same procedure as the above evaluation of COX-2's inhibition efficacy, but there is no pre-treatment of aspirin and LPS in the adhesion of macrophage.

<Table 4>

Example	Inhibition(%)					Example	Inhibition(%)				
	COX-2 (μg/mℓ)			COX-1 (μg/mℓ)			COX-2 (μg/mℓ)			COX-1 (μg/mℓ)	
	10	1	0.1	10	1		10	1	0.1	10	1
1		100	94	<5		39	86	31	11		
2	81	68	34	<5		40	69	29	6	<5	
3	72	61	13			41	96	36	<5	<5	
4	5<			<5		46	91	67	4		
5	100	90	39			47		86	23		
6	100	92	42			48		100	63	48	36
9	29	5<		<5		49	92	76	32		
10	86	67	14	<5		50	87	80	5		
11		89	46	<5		51	100	83	56	6	
14	71	32	18			52	99	96	73	67	62
15	90	83		13		53	92	90	76	61	52
16	24			<5		54		84	20	75	
17	13			<5		55	100	90		84	66
18	86	51		18		56	90	84	53	90	77
19	35	18		11		57		96	48	75	
20	85	<5		<5		58	96	63		60	34
21	55	35		<5		59		100	39		
22	90	82	14			60		100	43		
23	97	84	23			61		97	69	38	22
24	95	86	22			62		100	89	76	54
33	44	27		17		64	47	52	<5		
34	78	66		12		65	93	67		73	24
36	100	80	56	<5		66	90	83		80	40
37	88	76	47	<5		68		100	89	83	58
38	96	77	18			69	100	98	42	90	68

[Experimental example 2]

Regarding the compounds in some of the above Examples and indomethacin, depressant action on edema in mouse's ear and depressant action on edema in mouse's foot being induced by carrageenan are being measured by the following 2 methods. And the results of the depressant action on edema in mouse's ear and depressant action on edema in mouse's foot being induced by carrageenan

are shown in Table 5.

1. Measurement of depressant action on edama in mouse's ear

At 30 minutes after coating the left ear of ICR mouse, weighing 20g, with a solution of appropriate amount of sample in 20㎕ of mixed solvent DMSO : acetone(1:9), 25㎍ of TPA(tetradecanoylphorbol acetate) was coated on both ears. The determination of depressant action on edama was made in 5 hours later by the number of neutral granulocyte gathering in the ear after inducing TPA inflammation. The number of neutral granulocyte was estimated by measuring the activation of myeloperoxidase.

2. Measurement of depressant action on edama in mouse's foot induced by carrageenan

At 1 hour after oral administering to Male-Sprague-Dawley-white mouse, weighing 150 ~ 200 g, with a suspended solution of appropriate amount of sample in 0.5% of carboxymethyl cellulose and 0.2% of TWEN solution, edema on the right foot of mouse was induced by injecting 0.1㎖(1%) of carrageenan-saline solution. Right after the inducement of edema by carrageenan and 3 hours later, the edema rate was estimated by measuring white mouse's foot volume with Displacement Plethysmometer(Ugo Basile, Italy). Carrageenan injection Drug was administered 1 hour before the carrageenan injection. Depressant rate of edema is produced by the following equation 1.

[Equation 1]

% Depressant rate of edema =

$$(1-\Delta V_{\text{treated group}}/\Delta V_{\text{control group}}) \times 100$$

ΔV : change of foot volume

<Table 5>

	depressant rate of ear edema (ED50, % depressant rate)	depressant rate of edema rate induced by carrageenan(oral administration) (ED50, % depressant rate)
indomethacine	0.4 mg/ear, ED50	4.3 mg/kg, ED50 p.o.
Example 1	0.4 mg/ear, ED50	50mg/kg, 43% depression
Example 2	-	-
Example 3	1.2 mg/ear, ED50	50mg/kg, 52% depression
Example 5	-	-
Example 6	-	50mg/kg, 37% depression
Example 10	0.6 mg/ear, ED50	-
Example 11	-	30mg/kg, 17% depression
Example 12	0.4 mg/ear, ED50	30mg/kg, 20% depression
Example 14	-	-
Example 15		30mg/kg, 41% depression
Example 26	0.6 mg/ear, ED50	50mg/kg, 23% depression
Example 27	-	-
Example 28	0.8 mg/ear, ED50	-
Example 34		3mg/kg, 23% depression
Example 36	1.0 mg/ear, ED50	30mg/kg, 20% depression
Example 37		30mg/kg, 16% depression

As can be seen from the above Table 4, the compound(I) of the present invention has high selectivity on COX-2 so that it could inhibit the action of COX-2.

The present invention relates to the cyclooxygenase-2 inhibitor composition having one or more of which is selected from non-toxic, pharmaceutically acceptable carrier or adjuvant or diluent or other activating components with pharmaceutically effective amount of compound(I), and the composition of the present invention may be oil or could be in the form of solution, suspension or emulsion in aqueous medium or could be in the form of powder that is melted in sterile and pyrogen-free water before being used as oral formulation or parenteral formulation such as hypodermic injection, vein injection, intramuscular injection,

sternal injection, suppository or cream or gel or ointments or local formulation such as suspension, mouth washing.

In case of oral formulation, the composition of the present invention is prepared by the disclosed method of employing pharmaceutically acceptable carrier and excipient, for example, in the form of tablet, troches, saccharated tablet, aqueous or oily suspension, dispersive powder or particle, emulsion, soft or hard capsule, syrup, elixir, and it's stored by unit dosage or in multicapacity container.

The tablet, one of oral formulation, has the compound of the present invention mixed inactive additives which could be used in the preparation of tablet. The example may include, but not limited to, excipients such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, sodium phosphate or pelletizing agents such as corn, starch, alginic acid or disintegrating agents or coupling agents such as starch, gelatin, acacia or lubricants such as magnesium stearate, stearic acid, talc. The tablet is used without coating, or is used with coating to prevent absorption in gastrointestinal and disintegration of tablet. For example, time inhibitors such as glyceryl-mono-stearate or glyceryl-di-stearate is applicable. Hard capsule is a mixture of the compound of the present invention with solid diluent such as calcium carbonate, calcium phosphate, kaolin, and soft capsule is a mixture of the compound of the present invention with active components, which are mixtures of solvents such as water, mixable polyethyleneglycol, PEGs, ethanol with oil solvents such as peanut oil, liquid paraffin, olive oil.

Liquid suspensions is a mixture of active components with excipients, which is appropriate for preparation of liquid suspension. Excipinet for liquid suspensions is, for example, suspensions such as sodium carboxymethyl cellulose, methyl cellulose, hydroxy-propylmethyl cellulose, sodium alginic acid, polyvinyl-pyrrolidone, gum tragacanth, gum acacia or polyoxylenestearate which is a condensate of fatty acid and alkylene oxide or heptadecaethyleneoxycetanol which

is a condensate of long fatty acid and alkylene oxide; polyoxyethylenesorbitolmonoolate which is a condensate of hexitol anhydride and ester derived from fatty acid and ethylene oxide or humectants or dispersing agents. Liquid suspensions may further contain preservatives, colorants, condiments, sweeteners.

Oil suspensions is a mixture of vegetable oil such as olive oil, sesami oil or mineral oil such as liquid paraffin with active components, for example, it contains thickening agents such as beeswax, soft paraffin, cetyl alcohol. Also it contains preservatives, colorants, condiments, sweeteners, but such composition may contain antioxidants such as vitamin-c to improve shelf life.

Dispersive powder or particle contains active component in a mixture of dispersing agents, humectants, suspending agents and preservatives. The example of an adequate dispersing agent is humectants and suspending agents which are mentioned above. Additional excipient, for example, is sweeteners, condiments, colorants and etc.

Water in oil emulsion is a mixture of oil phase like vegetable oil such as olive oil or mineral oil such as liquid paraffin with emulsifier like natural phospholipid such as soy bean lecithin or sorbitanmonoolate, which is derived from hexitol anhydride or fatty acid ester, or reoxyethylenesorbitolmonoolate which is a condensate of hexitol anhydride and ester derived from fatty acid and ethylene oxide.

Syrup and elixir is a mixture of sweetener such as glycerol, propyleneglycol, sorbitol, sucrose with active components.

Parenteral formulation is injected in the form of suspension which is a mixture of sterile injectable solution or non-toxic, pharmaceutically acceptable diluting agents or solvents sucha as 1,3-butane-diol with active component. Available excipient or solvents is, for example, water, Ringer's solution and

isotonic sodium chloride solution. Cosolvent such as ethanol, polyethyleneglycol, polyprolyleneglycol is also available. Also, bland fixed oil could be commonly used as a solvent or a suspending solvent. And bland fixed oil for this purpose is used with synthetic mono-, di- glyceride. Also, fatty acid like oleic acid could be used in the preparation of injection. Suppository form is prepared by mixing with appropriate bland excipients such as cocoa butter and polyethyleneglycol, which keep suppository as solid form at room temperature and make suppository melt inside rectum. It is administered through rectum.

Local formulation generally consists of pharmaceutical carrier, auxiliary solvent, emulsifier, penetration accelerant, preservative and palliative.

In case of treating diseases with composition of the present invention, the dosage of active component of compound(I) depends on the patient's age, weight, general health condition, sex, meal, administration time, evacuation speed, drug combination, and severity of disease during treatment, but it could be used in the range of 0.01～140mg per 1kg(weight) per day according to the kind of diseases, or 0.5mg～7g per patient. For example, inflammation could be effectively treated with administering 0.01～50mg per 1kg(weight) or 0.5mg～3.5g per patient.

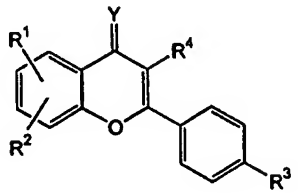
On the one hand, the amount of the compound of the present invention which would be mixed with carrier material to decide one formulation is different according to the way of administration paths and treating patients. For example, in formulation for oral administration to human, it consists of 5 ~ 95% of carrier materials and 0.5mg～5g of active components and in formulation for parenteral administration to human, it consists of 5～99% of carrier materials and 0.1mg～2.5g of active components in the oral administration.

It is understood that the foregoing detailed description is given merely by way of illustration and that modifications and variations may be therein without departing from the spirit and scope of the invention.

CLAIMS

1. A compound represented by the following general formula(I) :

(I)



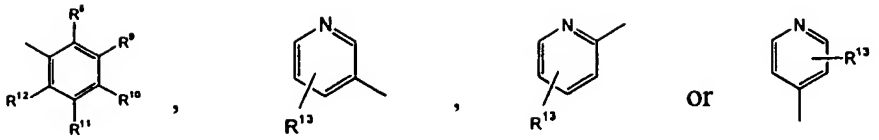
wherein

Y is an oxygen atom or a sulfur atom;

R^1 and R^2, identical to or different from each other, are independently a hydrogen atom, a halogen atom, a C_1 - C_6 lower alkyl group, a triflurometh yl group, an alkoxy group, a hydroxy group, a nitro group, a nitrile group, or a carboxyl group;

R^3 is a group of a formula : $S(O)nR^5$ wherein n is an integer of $0 \sim 2$, R^5 is a hydrogen atom, a C_1 -C_6 lower alkyl group, or a group of a formula : NR^6R^7 wherein R^6 and R^7, identical to or different from each other, are independently a hydrogen atom, or a C_1 -C_6 lower alkyl group; and

R^4 is oxazolyl, benzo[b]thienyl, furanyl, thienyl, naphthyl, thiazolyl, indolyl, pyrolyl, benzofuranyl, benzodioxolyl, or a substituted group presented by the following structures :



wherein

R^8 through R^{12}, identical to or different from one another, are independently a hydrogen atom, a halogen atom, a C_1 - C_6 lower alkyl group, a triflurometh yl group, an alkoxy group, a hydroxy group, a hydroxyalkyl group, a nitro group, a group of a formula : S(O)nR^5, a group of a formula : NR^6 R^7, a triflurometh oxy group, a nitrile group, a carboxyl group, an acetyl group, or a formyl group wherein n, R^5, R^6 and R^7 have the same meaning as defined X and R^3 above; and

R^{13} is a hydrogen atom, a halogen atom, a C_1 -C_6 lower alkyl group, a triflurometh yl group, a alkoxy group, a hydroxy group, a triflurometh oxy group, a carboxyl group, or an acetyl group;

or their pharmaceutically acceptable salts.

2. The compound (I) according to claim 1. which is

2-(4-(Methylsulfonyl)phenyl)-3-phenyl-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one,

3-(2-Methoxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-(N,N-Dimethylamino)phenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-(N-Methylamino)phenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(4-trifluoromethoxyphenyl)-4H-1-benzopyran-4-

one,

3-(3-Methoxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Isopropylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Ethylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Hydroxymethylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(4-trifluoromethylphenyl)-4H-1-benzopyran-4-one,

3-(4-Hydroxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2,3-Difluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(3,5-Difluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Hydroxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2,4-Difluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2,4-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Acetylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2,4-Dimethylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Formylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Carboxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Chloro-3-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Methoxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(3,4-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Fluorophenyl)-5-methoxy-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Fluorophenyl)-5-hydroxy-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-

one,

3-(3,5-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(N-methyl-3-pyrazolyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

6-Chloro-3-(4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4 -one,

2-(4-(methylsulfonyl)phenyl)-3-(3-nitrophenyl)-4H-1-benzopyran-4-one,

3-(3,4-Difluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

2-(4-(methylsulfonyl)phenyl)-3-(1-naphthyl)-4H-1-benzopyran-4-one,

3-(3-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(3-Chloro-4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Bromophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2,3-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(3-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(3-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(2-oxazolyl)-4H-1-benzopyran-4-one,

6-Fluoro-2-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Benzo[b]thienyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Chloro-5-pyridinyl)-7-fluoro-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

7-Fluoro-2-(4-(methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(2-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(4-pyridinyl)-4H-1-benzopyran-4-one,

6-Fluoro-2-(4-(methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-one,
7-Fluoro-3-(2-methoxy-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(1,3-Benzodioxol-5-yl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
2-(4-(Methylsulfonyl)phenyl)-3-(2-thiazolyl)-4H-1-benzopyran-4-one,
3-(Benzofuran-2-yl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
2-(4-(Methylsulfonyl)phenyl)-3-(2-thienyl)-4H-1-benzopyran-4-one,
2-(4-(Methylsulfonyl)phenyl)-3-(2-pyrazinyl)-4H-1-benzopyran-4-one,
3-(2-Methyl-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Methoxy-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
6-Fluoro-3-(2-methyl-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
6-Fluoro-3-(2-methoxy-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Chloro-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Chloro-5-pyridinyl)-6-fluoro-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Fluoro-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
6-fluoro-3-(2-fluoro-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
7-fluoro-3-(2-fluoro-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Chloro-3-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Fluorophenyl)-6-methoxy-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
2-(4-(Methylsulfonyl)phenyl)-3-(2-trifluoromethyl-5-pyridinyl)-4H-1-benzopyran-4-one,

3-(2-Fluoro-3-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Chloro-3-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(5-Bromo-3-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Furyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(5-Indanyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Fluorophenyl)-6-methyl-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4 -one,
3-(4-Fluorophenyl)-6-hydroxy-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4 -one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-methylphenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-phenyl-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(3,4-difluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(4-chloro-3-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(3-chloro-4-fluorophenyl)-4H-1-benzopyran-4-one,
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2-(4-(Aminosulfonyl)phenyl)-3-((4-methylthio)phenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-((3,4-methylenedioxy)phenyl)-4H-1-benzopyran-4 -one,
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2-(4-(Aminosulfonyl)phenyl)-3-(3,5-difluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-pyridinyl)-4H-1-benzopyran-4-one,
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2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(3-pyridinyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(3-pyridinyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-chloro-5-pyridinyl)-4H-1-benzopyran-4-one,
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2-(4-(Aminosulfonyl)phenyl)-3-(2-fluoro-5-pyridinyl)-4H-1-benzopyran-4-one,
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2-(4-(Aminosulfonyl)phenyl)-3-(2-methoxy-5-pyridinyl)-4H-1-benzopyran-4-one,
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2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(4-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-phenyl-4H-1-benzopyran-4-one,
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2-(4-(Aminosulfonyl)phenyl)-6-methoxy-3-(4-fluorophenyl)-4H-1-benzopyran-4-one,
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2-(4-(Aminosulfonyl)phenyl)-6-hydroxy-3-(4-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Methylsulfonyl)phenyl)-3-phenyl-4H-1-benzopyran-4-thione,
3-(4-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

6-Fluoro-3-(4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4 -thione,

3-(2-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

7-Fluoro-2-(4-(methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-thione,

3-(3-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(2-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(4-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(3-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(4-Methoxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

6-Fluoro-2-(4-(methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-thione,

3-(2-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(2,3-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(3,4-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(3-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(4-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(3-Methoxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

2-(4-(Methylsulfonyl)phenyl)-3-(4-trifluoromethylphenyl)-4H-1-benzopyran-4-thione,

3-(3-Chloro-4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4 -thione,

2-(4-(Methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-thione,

2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(3-pyridinyl)-4H-1-benzopyran-4-thione,

2-(4-(Aminosulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-thione,

2-(4-(Aminosulfonyl)phenyl)-3-(4-fluorophenyl)-4H-1-benzopyran-4-thione,

2-(4-(Aminosulfonyl)phenyl)-3-(2-fluorophenyl)-4H-1-benzopyran-4-thione,

2-(4-(Aminosulfonyl)phenyl)-3-(4-chlorophenyl)-4H-1-benzopyran-4-thione,

2-(4-(Aminosulfonyl)phenyl)-3-phenyl-4H-1-benzopyran-4-thione,

2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(4-fluorophenyl)-4H-1-benzopyran-4-thione,

2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(3-pyridinyl)-4H-1-benzopyran-4-thione

3. A cyclooxygenase-2 inhibitor composition comprising:

an effective amount of a compound according to claim 1 and a pharmaceutically acceptable salts thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00469

A. CLASSIFICATION OF SUBJECT MATTER

IPC[7]: C 07 D 311/30, 405/04, 413/04, 407/04, 409/04, 417/04; A 61 K 31/352, 31/4433

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: C 07 D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT, Chem.Abstr.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chemical Abstracts, Vol.68, No.19, 06 May 1968 (Columbus, Ohio, USA), page 8393, column 2, abstract No.87102k, G.Srimannarayana et al.:"Synthesis of 3-substituted flavones as potential insecticides", Symp.Syn.Heterocycl.Compounds Physiol.Interest, Hyderabad, India, 1964, 58-63 (1966).	1
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☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
23 September 1999 (23.09.99)	04 October 1999 (04.10.99)

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00469

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	The Patent Office Japanese Government PAJ CD-Rom 10[021], 31 October 1996 (31.10.96), Patent Abstracts of Japan unexamined Application, Publication number 08-157 361 (TOYAMA CHEM. CO., LTD.)	1,3
A	US 3 844 792 A (ZWEIG), 29 October 1974 (29.10.74).	1
A	WO 96/13 500 A (MERCK FROSST CANADA), 09 May 1996 (09.05.96), claims 4,8.	1,3
A	WO 96/06 840 A (MERCK FROSST CANADA), 07 March 1996 (07.03.96), cited in the application.	1,3

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 99/00469

In Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
US A 3844792	29-10-1974	keine - none - rien	
WO A 9613500		keine - none - rien	
WO A 9606840		keine - none - rien	

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(54) Title: PHARMACEUTICAL COMPOSITION AND METHOD FOR TREATMENT OF INFLAMMATION

(57) Abstract

The present invention relates to pharmaceutical compositions comprising enantiomerically pure R–NSAIDs and the methods of their use for the treatment of inflammation. Preferably, the R–NSAID used is R–flurbiprofen which is administered in a dose of at least 2.5 milligrams per kilogram of body weight per day. The anti–inflammatory action of R–NSAIDs is due to their ability to interfere with the biosynthesis of COX–2 by inhibiting COX–2 mRNA synthesis, rather than by just blocking the action of the enzyme itself. In order to effect the inhibition of COX–2 mRNA synthesis, the R–NSAID must be present at relatively high doses. Because the R–NSAID is selective in its action, that is it does not inhibit either COX–1 mRNA synthesis or the COX–1 enzyme itself, it can be administered in the required high doses because the tissue protective effects of prostaglandins made through the COX–1 pathway are not interfered with.

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PHARMACEUTICAL COMPOSITION AND METHOD FOR TREATMENT OF INFLAMMATION

Field of the Invention

The present invention relates to pharmaceutical compositions comprising enantiomerically pure R-NSAIDs and the methods of their use for the treatment of inflammation. Preferably, the R-NSAID used is R-flurbiprofen which is administered in a dose of at least 2.5 milligrams per kilogram of body weight per day.

Background of the Invention

Nonsteriodal anti-inflammatory drugs (NSAIDs) have been in use for over a century beginning with aspirin. In recent decades the arylpropionic acid (APA) class of these drugs has gained wide acceptance.

Although the NSAIDs are known to be effective against pain and inflammation, there are often severe side effects and toxicity associated with chronic use of these drugs. Chronic NSAID use is known to cause gastric and duodenal ulceration, which may be severe enough to result in significant morbidity and mortality. Furthermore, NSAID use has been reported to be associated with renal and hepatic toxicities, increase in bleeding times due to disruption of platelet function, prolongation of gestation due to uterine effects, and a decreased white cell count in the blood. Because of the side effects and toxicity, many NSAIDs are no longer in use in human medicine as analgesics. Some of these include tiaprofenic acid, suprofen, carprofen, pirprofen, benoxaprofen, and indoprofen.

Some NSAIDs, including the APAs, exhibit molecular chirality and thus have R- and S-enantiomers. The APAs, with the exception of naproxen, are currently prescribed as racemates.

For a given NSAID, there can be a difference in the properties exhibited by the R- and S-enantiomers. One important difference relates to the activities of the two enantiomers in connection with prostaglandin synthesis.

Prostaglandins are autocoids, produced by the body, which serve a variety of functions. An important step in the biosynthesis of prostaglandins requires the use of two cyclooxygenase (COX) enzymes, COX-1 or COX-2. COX-1 is present throughout the body and makes the prostaglandins that, among other things, help keep the stomach lining intact and the aid proper function of the kidneys. COX-2 is made by the body only under certain conditions, such as in response to tissue injury, and the prostaglandins produced by it are associated with pain and inflammation.

Researchers found that the S-enantiomers of NSAIDs were much better at inhibiting prostaglandin synthesis than the R-enantiomer, having 15-100 or even 500 times higher prostaglandin synthetase inhibitory activities than the R-enantiomers in the rat. Yamaguchi et al., Nippo Yakurigaku Zasshi, 90:295-302 (1987). Thus, it was thought that the biological activity of NSAIDs resided prinipally if not only in the S-enantiomers. Some researchers went as far as to say that "at best, the R-isomers [of APAs] function as prodrugs for the therapeutically active S-forms" when the racemic drug is administered to the host, and that the R-enantiomers are "undesirable impurities in the active drug." Caldwell et al., Biochem. Pharmacol. 37:105-114 (1988).

Although the S-NSAIDs have the desired effect of inhibiting production of prostaglandins through the COX-2 pathway, they also inhibit the production through the COX-1 pathway and thus the bad side effects of NSAID use generally are also associated with the use of S-enantiomers.

Earlier studies by researchers in this field, as well as by the inventor himself, found that R-NSAIDs had little or no inhibiting effect on COX enzymes and prostaglandin production. What little anti-inflammatory effect existed was either found to be statistically insignificant or attributed to the S-enantiomer, the presence of which was due to either an enantiomerically impure dose of R-NSAID or inversion of the R-enantiomer in vivo. See K. Brune et al, Pure Enantiomers of 2-Arylpropionic Acids: Tools in Pain Research and Improved Drugs in Rheumatology, J. Clin. Pharmacol. 32:944-52, 946 (1992); K. Brune et al., Aspirin-like drugs may block pain independently of prostaglandin synthesis inhibition, Experentia 47:257-61, 260 (1991); U.S. Patent No. 5,200,198 to Geisslinger et al.; and U.S. Patent No. 5,206,029 to Brune et al.

Although the researchers did not find significant anti-inflammatory activity, there was evidence of other activity attributable to the R-enantiomer, such as amelioration of pain (see U.S. Patent Nos. 5,200,198 and 5,206,029), treatment and prevention of cancer (see Wechter et al., R-Flurbiprofen Chemoprevention and Treatment of Intestinal Adenomas in the $APC^{Min}/+$ Mouse Model, Cancer Research 57:4316-24 (1997)), treatment of cystic fibrosis (see U.S. Patent Application Serial No. 09/058,093) and treating or delaying the onset of Alzheimer's Disease (see U.S. Patent Application Serial No. 08/814,490).

U.S. Patent Nos. 5,200,198 and 5,206,029 disclose the use of mixtures of R- and S-flurbiprofen to treat diseases characterized by pain and/or inflammation. The inventors state that R-flurbiprofen has better pain amelioration activity than S-flurbiprofen, and that the known side effects are coupled with the anti-inflammatory effects in S-flurbiprofen. Thus, according to the inventions, if one were to create a medicament for the treatment of a disease that was characterized primarily by pain, one would use a mixture having an excess of the R-flurbiprofen, so as to maximize the effects against pain. The amount of S-flurbiprofen in the mixture would be minimized, so as to attain a balance between the needed anti-inflammatory activity and the undesired side effects which result from use of the S-enantiomer. If, according to the disclosures of the '198 and '029 patents, one wanted to create medicament for the treatment of a disease characterized by both pain and inflammation, one would increase the amount of S-flurbiprofen in the composition in order to have the needed anti-inflammatory effect and would have to accept the unwanted side effects.

A common test which is used to determine whether a compound has activity as an anti-inflammatory drug is the carrageenan paw test. In this test, the test compound is administered to several rats. Thereafter, a paw on each rat is injected with a solution of carrageenan in order to induce edema in the paw as a measure of inflammation. After three hours, the volume of the paw is measured using a plethysmometer. Reduction of edema by 30% or more, as compared to a control group which was not given the test compound, is considered indicative of anti-inflammatory activity.

In the '198 and '029 patents, there is described the results of the carrageenan paw test done using a dosage of 0.3 mg/kg of R- or S- flurbiprofen. The enantiomeric purity of the compounds used is not disclosed. For these tests, it was reported that the reduction of edema for the S-flurbiprofen was 64%, indicating anti-inflammatory activity, but for the R-flurbiprofen it was only 18% which does not indicate anti-inflammatory activity.

The inventors in the '198 and '029 patents, Brune and Geisslinger, later reported carrageenan paw tests using dosages of approximately 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, and 2.5 mg/kg of R- and S-flurbiprofen (Experentia, 47:257-261). Only at the highest dose, 2.5 mg/kg, did the R-flurbiprofen demonstrate a statistically significant reduction in inflammation.

In a 1996 article entitled New Insights into the Site and Mode of Antinociceptive Action of Flurbiprofen Enantiomers (J. Clin. Pharmcol. 36:513-20), Brune and Geisslinger discussed the tests first reported in the Experentia article, stating that: "as expected, only the S-enantiomer had antiinflammatory activity. The antiinflammatory effects after administration of higher doses of R-flurbiprofen may be explained by an S- impurity of the administered R-enantiomer (purity: S-flurbiprofen, 98.5%; R-flurbiprofen, 99.1%) and/or by small amounts of S-flurbiprofen formed by inversion."

More recently, following the discovery of the differences between COX-1 and COX-2, some drug companies have set forth to make compounds which selectively inhibit COX-2, so as to achieve the desired anti-inflammatory and analgesic effects while avoiding the toxic effects associated with COX-1 inhibition. Some of these recent advances were discussed in a recent article in Science (Elizabeth Pennisi, "Building A Better Aspirin", Science 280:1191-92 (1988), and have even found their way to the mainstream media such as Jerome Groopman's article entitled "Superaspirin" (The New Yorker p.32-35 (1998)). These articles present the new COX-2 inhibitor drugs as far superior to the older NSAIDs and state that this new class of COX-2 inhibitors will eventually replace the older NSAIDs, which will "become dinosaurs." This current flurry of research and media activity makes it clear that a need remains for an anti-inflammatory compound characterized by an ability to selectively block prostaglandin production via the COX-2 pathway.

Summary of the Invention

There is provided in accordance with one aspect of the present invention, a method of treating inflammation in an animal. The method comprises administering to the animal a dose of at least 2.5 milligrams of an enantiomerically pure R-NSAID per kilogram of said animal's body weight. In other embodiments, the administered dose is at least 5 mg/kg, at least 25 mg/kg, and at least 50mg/kg of the animals body weight. In preferred embodiments of the methods, the R-NSAID is selected from the group consisting of R-ketoprofen, R-flurbiprofen, R-ketorolac, R-etodolac, R-tiaprofenic acid, R-suprofen, R-carprofen, R-pirprofen, and R-benoxaprofen. In an especially preferred embodiment, the R-NSAID is R-flurbiprofen.

In accordance with a further aspect of the present invention, there is provided a pharmaceutical composition for the treatment of inflammation. The pharmaceutical composition comes in a unit dosage form and comprises at least 200 milligrams of an enantiomerically pure R-NSAID. In other embodiments, the unit dosage form is at least 400 milligrams, at least 1,000 milligrams, and at least 3,500 milligrams. In preferred embodiments, the R-NSAID of the pharmaceutical composition is selected from the group consisting of R-ketoprofen, R-flurbiprofen, R-ketorolac, R-etodolac, R-tiaprofenic acid, R-suprofen, R-carprofen, R-pirprofen, and R-benoxaprofen. In an especially preferred embodiment, the R-NSAID is R-flurbiprofen.

Detailed Description of the Preferred Embodiment

Although NSAIDs have been known for many years as anti-inflammatory drugs, the activity was believed to lie in the S-enantiomer only, due to its ability to inhibit the COX-2 enzyme. The R-enantiomer exhibits only minor inhibition of the COX-2 enzyme, and was thus believed to be inactive as an anti-inflammatory agent, though it was found to have utility for other indications.

It has surprisingly been found by the inventor herein that R-NSAIDs have anti-inflammatory activity when given at relatively high dosages, that is more than 2.5 mg/kg. The anti-inflammatory properties of R-NSAIDs is due to their ability to interfere with the biosynthesis of COX-2 by inhibiting COX-2 mRNA synthesis, rather than by just blocking the action of the enzyme itself. In order to effect the inhibition of COX-2 mRNA synthesis, the R-NSAID must be present at relatively high concentrations. Because the R-NSAID is selective in its action, that is it does not significantly inhibit either COX-1 mRNA synthesis or either of the COX enzymes themselves, it can be administered in the required high doses because the tissue protective effects of prostaglandins made through the COX-1 pathway are not interfered with.

Because of the unpleasant and undesirable side effects associated with the S-enantiomers, it is desired that the R-NSAIDs used in the pharmaceutical compositions and methods of the present invention be substantially free of the S-enantiomer, that is "enantiomerically pure." An enantiomerically pure R-NSAID, as that term is used herein, comprises preferably at least 98% R-NSAID, more preferably at least 99.5% R-NSAID, most preferably at least 99.9% R-NSAID.

For the methods and pharmaceutical compositions of the present invention, the enantiomerical purity is in reference to the R-NSAID as it exists prior to being administered to the animal host or patient. This is because both S- and R-arylpropionic acid NSAIDs are subject to interconversion by means of inversion when placed in vivo. The degree of inversion varies widely among the NSAIDs and is generally different for the R- and S- enantiomeric forms of a given compound. The degree of inversion for a given enantiomer may also vary by the dose given, the species of animal tested, the gender of animal tested, and the amount of time the enantiomer has been in the animal's system.

Preferred R-NSAIDs for use in the methods and pharmaceutical compositions of the present invention are those which are enantiomerically stable. As used herein, "enantiomerically stable" means that at a steady state, there is preferably no more than about 10% of the S-enantiomer of the NSAID in circulation, more preferably no more than 2%, most preferably no more than about 1% of the S-enantiomer in circulation, the S-enantiomer having been formed in vivo from inversion of the R-enantiomer. Examples of enantiomerically stable R-NSAIDs are R-flurbiprofen (1.5% S-enantiomer in circulation at steady state in humans), R-ketoprofen (10% S), R-ketorolac (6% S), and R-etolodac (0% S).

A large number of R-NSAIDs which are preferred for use in the medicaments and methods of the present invention are commercially available. The enantiomeric purity of any given R-NSAID may vary among manufacturers. R-ketoprofen, R-flurbiprofen, and R-ketorolac are available through Sepracor, Inc. (Marlborough, MA); R-naproxen can be obtained as a sodium salt through Sigma Chemical Co.; R-etodolac is available from Wyeth-Ayerst; R-tiaprofenic acid is available through Roussel (France); R-suprofen is manufactured by McNiel Pharmaceuticals; R-carprofen is available from Roche (Switzerland); R-pirprofen is available through Carlo Elba (Italy); and R-benoxaprofen is manufactured by Eli Lilly and Co. (Indianapolis, IN). Additionally, racemates which can be resolved by methods known in the art, may be obtained from several of the above sources.

The most preferred R-NSAID for use in the methods and pharmaceutical compositions of the present invention is R-flurbiprofen, based on its superior enantiomeric stability in humans and availability in a very enantiomerically pure form, up to 99.97%.

This very pure form of R-flurbiprofen, was tested for anti-inflammatory activity by the carrageenan paw test. Seven groups of eight male Long Evans derived rats weighing 150 20 grams were fasted overnight. One hour after oral administration a suspension of the test substance in 2% Tween 80, as documented in Table 1 below, the right hind paw of each rat was injected intraplantarly with 0.1 ml of a 1% suspension of carrageenan. Three hours after injection, the hind paw volume was measured using a plethysmometer and recorded.

Table 1.

RESULTS OF CARRAGEENAN PAW TEST			
Substance Tested	Dose	Result (Reduction of Edema)	Anti-Inflammatory Activity
Vehicle (2% Tween 80)	10 ml/kg	0%	No
Positive Control (Aspirin)	150 mg/kg	42%	Yes
R-Flurbiprofen	40 mg/kg	51%	Yes
R-Flurbiprofen	20 mg/kg	47%	Yes
R-Flurbiprofen	10 mg/kg	41%	Yes
R-Flurbiprofen	5 mg/kg	30%	Yes

As seen in Table 1 above, R-flurbiprofen present at high doses exhibits anti-inflammatory action, that is it causes a statistically significant reduction of edema in the rat.

The pharmaceutical compositions of the present invention can be prepared in any desired form, for example, tablets, powders, capsules, sterile suspensions or solutions for parenteral administration, non-sterile suspensions or solutions for oral administration, suppositories, aerosols, and the like. Furthermore, the pharmaceutical compositions of the present invention may be administered by any route including oral, intravenous, intramuscular, vaginal, rectal, topical, transdermal, buccal, nasal, inhalation, and the like. The use of controlled release means and other drug delivery devices are contemplated by the inventor.

In addition to one or more R-NSAIDs, the pharmaceutical compositions of the present invention may optionally comprise carriers, fillers, diluents, granulating agents, lubricants, binders, disintegrating agents, release agents and the like. Preferred fillers include starch, glucose, lactose, mannitol, calcium phosphate, calcium carbonate, and cellulose. Preferred lubricants include talc, calcium stearate, and magnesium stearate. Preferred release agents include carboxymethyl cellulose, carboxymethyl starch, polyvinylpyrrolidone (PVP), and silica gel. Which optional ingredients are present and the quantity used is dependent upon many factors, including the form the medicament will take, the desired strength of the

final composition, and the desired speed at which the active ingredients are to be released into the animal's system. It is within the abilities of one skilled in the art to create a suitable formulation for use in methods of the present invention, including the choice of optional ingredients and the amounts in which they are present.

The R-NSAIDs used in the methods and pharmaceutical compositions of the present invention may be present in the form of a pharmaceutically acceptable salt. When describing formulations used in the methods and compositions of the present invention, R-NSAID should be read as also including any of the pharmaceutically acceptable salts thereof. The term "pharmaceutically acceptable salt" as used herein refers to salts prepared from pharmaceutically acceptable, non-toxic acids or bases. Suitable pharmaceutically acceptable salts include inorganic salts, e.g. salts of aluminum, calcium, lithium, magnesium, potassium, sodium and zinc, or organic salts, e.g. salts of lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine, procaine, and tris. A salt may be chosen to effect a particular rate of dissolution or uptake in the body, as is known in the art.

Of the available routes, the oral route is preferred, and oral solid preparations (e.g. tablets, capsules, caplets, powders, chewable tablets) are preferred over oral liquid preparations. The most preferred oral solid preparations are tablets. A common method of forming a suitable pressed tablet is to combine the powdered active material having a suitable particle size distribution with pharmaceutically compatible adjuvants, such as lubricants, inert diluents, dispersing agents, carriers binders, and the like, and then press the mixture in a suitable machine. Molded tablets may be made by molding the composition, which preferably comprises a mixture of powdered material comprising at least one R-NSAID and any optional adjuvants, moistened with an inert liquid diluent in a suitable molding machine as is known in the art. Molded tablets may also contain any optional material such as those described above. If the tablets are in chewable form, addition of one or more flavorings and sweeteners, such as saccharin, is preferred.

Another form for the oral route is the capsule. Capsules, preferably made of gelatin, may be filled with dry materials such as powder, granules and pellets or with a suspension such as that formed by mixing the R-NSAID with a material such as vegetable oil or other pharmaceutically compatible carrier.

Oral suspensions and solutions for use in the present invention preferably comprise at least one R-NSAID, water, sweetener (such as sugar, saccharin, or aspartame), a flavoring (such as mint, or any of the known FDA-approved artificial flavorings), and a suspension or emulsifying agent (such as Tween or tragacanth). Preferably such suspensions or solutions are made by first combining all ingredients other than the R-NSAID, and then mixing in a sufficient quantity of finely powdered R-NSAID to achieve a solution or suspension of desired strength.

Injectable solutions are preferably prepared by combining a salt of the R-NSAID with water or isotonic saline. Other materials such as preservatives, sugars, and other drugs may be added on an optional basis. After mixing, the solution is filtered and placed in a sterile container, such as a vial or plastic infusion bag. The concentration of the solution can vary widely, depending upon whether such solution is to be infused to a patient over time or administered via a single hypodermic injection.

The dose of R-NSAID may also take the form of a suppository for either rectal or vaginal administration. A suitable suppository composition comprises the active ingredient (R-NSAID) mixed with a carrier, such as a fat or

polyglycol, having a melting point at or near body temperature. Alternatively, the carrier may be a material which dissolves when placed in the rectum or vagina. The suppository is preferably made by mixing powdered R-NSAID with the carrier, and then forming the mixture into a generally cylindrical or bullet shape of a size which allows for insertion.

Other dosage forms can be prepared by one skilled in the art by the use of known or later developed techniques which allow for the administration of a solid substance to an animal.

The quantity of R-NSAID used in the pharmaceutical compositions and methods of the present invention is dependent upon the body weight of the animal to whom the drug is administered and the frequency of dosing. It is preferred that the total daily dose for anti-inflammatory effect be at least 2.5 milligrams of R-NSAID per kilogram of body weight of the animal (2.5 mg/kg), preferably at least 5 mg/kg, more preferably 25 - 50 mg/kg or more. As the compounds and compositions of the present invention are not toxic, it is not foreseen that there is an upper limit to the dose at which the compounds of the present invention can be given. A dose comprising several grams of an R-NSAID is contemplated by the inventor.

The total quantity of dose may also be dependent upon the form which the dose takes and the relative efficiency or inefficiency of delivery of the drug by that particular dose form or route. For example, to achieve the same concentration of the drug in the body of the animal, it may be necessary to deliver a larger dose when a drug is administered via a relatively inefficient means such as a suppository or inhalation, as opposed to when the drug is administered by a more efficient method such as intravenous injection or orally.

The preferred total daily dose may be administered in a single dose or in smaller doses administered two, three, four, or more times during the day which, when summed together, equal the total daily dose. If a drug delivery device such as a transdermal patch is used, the dose may be administered continually over a period of hours. The determination as to whether and to what extent the total daily dose should be broken down into smaller doses administered throughout the day is dependent on several factors, including the half-life of the particular R-NSAID in the body, the speed at which the form of the R-NSAID becomes biologically available, and the total quantity of R-NSAID which needs to be administered.

Although the present invention has been described in terms of certain preferred embodiments, it is to be understood that the scope of the invention is not to be limited thereby. Instead, Applicant intends that the scope of the invention be limited solely by reference to the attached claims, and that variations on the formulation and dosages disclosed herein which are apparent to those of skill in the art will fall within the scope of Applicant's invention.

WHAT IS CLAIMED IS:

1. A method of treating inflammation in an animal, comprising administering to said animal a dose of at least 2.5 milligrams of an enantiomerically pure R-NSAID per kilogram of said animal's body weight.

2. The method of Claim 1 wherein said dose is at least 5 milligrams of an enantiomerically pure R-NSAID per kilogram of said animal's body weight.

3. The method of Claim 1 wherein said dose is at least 25 milligrams of an enantiomerically pure R-NSAID per kilogram of said animal's body weight.

4. The method of Claim 1 wherein said dose is at least 50 milligrams of an enantiomerically pure R-NSAID per kilogram of said animal's body weight.

5. The method of Claim 1 wherein said R-NSAID is selected from the group consisting of R-ketoprofen, R-flurbiprofen, R-ketorolac, R-etodolac, R-tiaprofenic acid, R-suprofen, R-carprofen, R-pirprofen, and R-benoxaprofen.

6. The method of Claim 1 wherein said R-NSAID is R-flurbiprofen.

7. A pharmaceutical composition for the treatment of inflammation in a unit dosage form comprising at least 200 milligrams of an enantiomerically pure R-NSAID.

8. The pharmaceutical composition of Claim 7, wherein said unit dosage form comprises at least 400 milligrams.

9. The pharmaceutical composition of Claim 7, wherein said unit dosage form comprises at least 1,000 milligrams.

10. The pharmaceutical composition of Claim 7, wherein said unit dosage form comprises at least 3,000 milligrams.

11. The pharmaceutical composition of Claim 7, wherein said unit dosage form comprises at least 5,000 milligrams.

12. The pharmaceutical composition of Claim 7 wherein said R-NSAID is selected from the group consisting of R-ketoprofen, R-flurbiprofen, R-ketorolac, R-etodolac, R-tiaprofenic acid, R-suprofen, R-carprofen, R-pirprofen, and R-benoxaprofen.

13. The pharmaceutical composition of Claim 7 wherein said R-NSAID is R-flurbiprofen.